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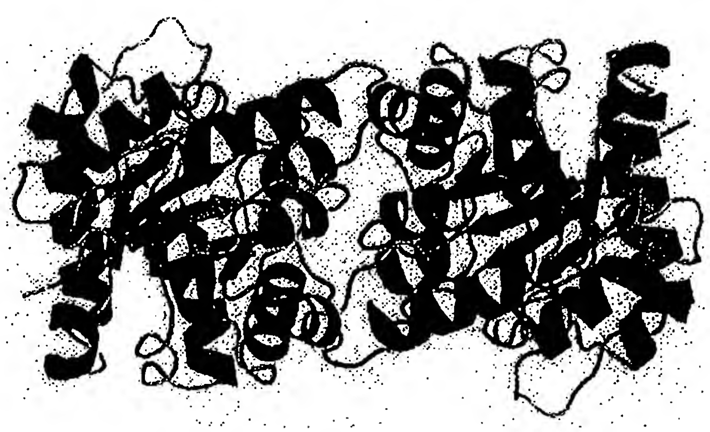
(54) Title: NOVEL PURIFIED POLYPEPTIDES FROM *PSEUDOMONAS AERUGINOSA*



(57) Abstract: The present invention relates to novel drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

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Novel Purified Polypeptides from Pseudomonas aeruginosa

RELATED APPLICATION INFORMATION

This application claims the benefit of priority to the following U.S. Provisional Patent Applications, all of which applications are hereby incorporated by reference in their entirety.

Provisional Application Number	*Filing Date*
60/324,739	September 25, 2001
60/376,917	May 1, 2002

INTRODUCTION

The discovery of novel antimicrobial agents that work by novel mechanisms is a problem researchers in all fields of drug development face today. The increasing prevalence of drug-resistant pathogens (bacteria, fungi, parasites, etc.) has led to significantly higher mortality rates from infectious diseases and currently presents a serious crisis worldwide. Despite the introduction of second and third generation antimicrobial drugs, certain pathogens have developed resistance to all currently available drugs.

One of the problems contributing to the development of multiple drug resistant pathogens is the limited number of protein targets for antimicrobial drugs. Many of the antibiotics currently in use are structurally related or act through common targets or pathways. Accordingly, adaptive mutation of a single gene may render a pathogenic species resistant to multiple classes of antimicrobial drugs. Therefore, the rapid discovery of drug targets is urgently needed in order to combat the constantly evolving threat by such infectious microorganisms.

Recent advances in bacterial and viral genomics research provides an opportunity for rapid progress in the identification of drug targets. The complete genomic sequences for a number of microorganisms are available. However, knowledge of the complete genomic sequence is only the first step in a long process toward discovery of a viable drug target. The genomic sequence must be annotated to identify open reading frames (ORFs), the essentiality of the protein encoded by the ORF must be determined and the mechanism of action of the gene product must be determined in order to develop a targeted approach to drug discovery.

There are a variety of computer programs available to annotate genomic sequences. Genome annotation involves both identification of genes as well assignment of function thereto based on sequence comparison to homologous proteins with known or predicted functions. However, genome annotation has turned out to be much more of an art than a science. Factors such as splice variants and sequencing errors coupled with the particular algorithms and databases used to annotate the genome can result in significantly different annotations for the same genome. For example, upon reanalysis of the genome of *Mycoplasma pneumoniae* using more rigorous sequence comparisons coupled with molecular biological techniques, such as gel electrophoresis and mass spectrometry, researchers were able to identify several previously unidentified coding sequences, to dismiss a previous identified coding sequence as a likely pseudogene, and to adjust the length of several previously defined ORFs (Dandkar et al. (2000) Nucl. Acids Res. 28(17): 3278-3288). Furthermore, while overall conservation between amino acid sequences generally indicates a conservation of structure and function, specific changes at key residues can lead to significant variation in the biochemical and biophysical properties of a protein. In a comparison of three different functional annotations of the *Mycoplasma genitalium* genome, it was discovered that some genes were assigned three different functions and it was estimated that the overall error rate in the annotations was at least 8% (Brenner (1999) Trends Genet 15(4): 132-3). Accordingly, molecular biological techniques are required to ensure proper genome annotation and identify valid drug targets.

However, confirmation of genome annotation using molecular biological techniques is not an easy proposition due to the unpredictability in expression and purification of polypeptide sequences. Further, in order to carry out structural studies to validate proteins as potential drug targets, it is generally necessary to modify the native proteins in order to facilitate these analyses, e.g., by labeling the protein (e.g., with a heavy atom, isotopic label, polypeptide tag, etc.) or by creating fragments of the polypeptide corresponding to functional domains of a multi-domain protein. Moreover, it is well-known that even small changes in the amino acid sequence of a protein may lead to dramatic affects on protein solubility (Eberstadt et al. (1998) Nature 392: 941-945). Accordingly, genome-wide validation of protein targets will require considerable effort even in light of the sequence of the entire genome of an organism and/or purification conditions for homologs of a particular target.

We have developed reliable, high throughput methods to address some of the shortcomings identified above. In part, using these methods, we have now identified, expressed, and purified a novel antimicrobial target from *Pseudomonas aeruginosa*, or *P. aeruginosa*. Various biophysical, bioinformatic and biochemical studies have been used to characterize the structure and function of the polypeptides of the invention.

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SUMMARY OF THE INVENTION

As part of an effort at genome-wide structural and functional characterization of microbial targets, the present invention provides polypeptides from *P. aeruginosa*. In

various aspects, the invention provides the nucleic acid and amino acid sequences of the polypeptides of the invention. The invention also provides purified, soluble forms of the polypeptides of the invention suitable for structural and functional characterization using a variety of techniques, including, for example, affinity chromatography, mass spectrometry, NMR and x-ray crystallography. The invention further provides modified versions of the polypeptides of the invention to facilitate characterization, including polypeptides labeled with isotopic or heavy atoms and fusion proteins.

A polypeptide of the invention has been crystallized and its structure solved as described in detail below, thereby providing information about the structure of the polypeptide, and druggable regions, domains and the like contained therein, all of which may be used in rational-based drug design efforts.

In general, the biological activity of a polypeptide of the invention is expected to be characterized as having a biochemical activity substantially similar to that of triosephosphate isomerase ("TIM"), having the gene designation of *tpiA*, as described in more detail below. This assignment has been confirmed by solving the X-ray structure of a polypeptide of the invention.

All of the information learned and described herein about the polypeptides of the invention may be used to design modulators of one or more of their biological activities. In particular, information critical to the design of therapeutic and diagnostic molecules, including, for example, the protein domain, druggable regions, structural information, and the like for the polypeptides of the invention is now available or attainable as a result of the ability to prepare, purify and characterize them, and domains, fragments, variants and derivatives thereof.

In other aspects of the invention, structural and functional information about the polypeptides of the invention has and will be obtained. Such information, for example, may be incorporated into databases containing information on the polypeptides of the invention, as well as other polypeptide targets from other microbial species. Such databases will provide investigators with a powerful tool to analyze the polypeptides of the invention and aid in the rapid discovery and design of therapeutic and diagnostic molecules.

In another aspect, modulators, inhibitors, agonists or antagonists against the polypeptides of the invention, or biological complexes containing them, or orthologues thereto, may be used to treat any disease or other treatable condition of a patient (including

humans and animals), and particularly a disease caused by *P. aeruginosa*, such as, for example, one of the following: osteomyelitis, otitis externa, conjunctivitis, keratitis, endophthalmitis, alveolar necrosis, vascular invasion, bacteremia, and burn infection.

The present invention further allows relationships between polypeptides from the same and multiple species to be compared by isolating and studying the various polypeptides of the invention and other proteins. By such comparison studies, which may involve multi-variable analysis as appropriate, it is possible to identify drugs that will affect multiple species or drugs that will affect one or a few species. In such a manner, so-called "wide spectrum" and narrow spectrum" anti-infectives may be identified. Alternatively, drugs that are selective for one or more bacterial or other non-mammalian species, and not for one or more mammalian species (especially human), may be identified (and vice-versa).

In other embodiments, the invention contemplates kits including the subject nucleic acids, polypeptides, crystallized polypeptides, antibodies, and other subject materials, and optionally instructions for their use. Uses for such kits include, for example, diagnostic and therapeutic applications.

The embodiments and practices of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, figures and claims that follow, with all of the claims hereby being incorporated by this reference into this Summary.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows the nucleic acid coding sequence for an exemplary polypeptide of the invention as predicted from the genomic sequence of *P. aeruginosa* (SEQ ID NO: 1). This predicted nucleic acid coding sequence was cloned and sequenced to produce the polynucleotide sequence shown in FIGURE 3 (SEQ ID NO: 3).

FIGURE 2 shows the amino acid sequence for an exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 1 (SEQ ID NO: 2).

FIGURE 3 shows the experimentally determined nucleic acid coding sequence for an exemplary polypeptide of the invention (SEQ ID NO: 3).

FIGURE 4 shows the amino acid sequence for the exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 3 (SEQ ID NO: 4).

FIGURE 5 shows the primer sequences used to amplify the nucleic acid of SEQ ID NO: 3. The primers are SEQ ID NO: 5 and SEQ ID NO: 6.

FIGURE 6 contains Table 1, which provides among other things a variety of data and other information on the polypeptides of the invention.

FIGURE 7 contains Table 2, which provides the results of several bioinformatic analyses relating to SEQ ID NO: 2.

FIGURE 8 contains Table 3, which shows information related to the x-ray structure for a polypeptide of the invention as described more fully in EXAMPLE 15.

FIGURE 9 lists the atomic structure coordinates for a polypeptide of the invention derived from x-ray diffraction from a crystal of such polypeptide, as described in more detail in EXAMPLE 15. There are multiple pages to FIGURE 9, labeled 1, 2, 3, etc. The information in such Figure is presented in the following tabular format, with a generic entry provided as an example:

Record Header	No.	Atom Type	Resi -due	Residue Number	X	Y	Z	OCC	B
ATOM 1	1	CB	HIS	1	4.497	15.607	34.172	1	70.54

In the table, "Record Header" describes the row type, such as "ATOM". "No." refers to the row number. The first "Atom Type" column refers to the atom whose coordinates are measured, with the first letter in the column identifying the atom by its elemental symbol and the subsequent letter defining the location of the atom in the amino acid residue or other molecule. "Residue" and "residue number" identifies the residue of the subject polypeptide. "X, Y, Z" crystallographically define the atomic position of the atom measured. "Occ" is an occupancy factor that refers to the fraction of the molecules in which each atom occupies the position specified by the coordinates. A value of "1" indicates that each atom has the same conformation, i.e., the same position, in all molecules of the crystal. "B" is a thermal factor that is related to the root mean square deviation in the position of the atom around the given atomic coordinate.

FIGURE 10 depicts a clustal V-based sequence alignment of the triosephosphate isomerase protein sequences from six pathogens. The dark shading indicates conserved amino acids across species, with gray areas less conserved.

FIGURE 11 depicts a schematic ribbon diagram of the structure of *P. aeruginosa* triosephosphate isomerase dimer in a side-on view, showing the β barrel architecture. The

shading scheme is used to provide depth perception, with dark representing near objects and light for distant objects.

FIGURE 12 depicts a schematic ribbon diagram of a *P. aeruginosa* triosephosphate isomerase dimer, viewed down the barrel axis.

FIGURE 13 depicts the residues located in and around the catalytic site of yeast TIM complexed with the transition state analogue 2-phosphoglycolic acid (2-PGA). The catalytic residues (E165, H95) at the active site as well as those that anchor the substrate (magenta) are shaded dark and light blue, respectively. The 11-residue flexible loop that appears to "close" the active site upon binding of the substrate to the enzyme is colored red. The residues (A176 and Y208) thought essential for proper closure of the loop are colored green.

FIGURE 14 depicts a schematic ribbon diagram of *P. aeruginosa* TIM illustrating the "open" conformation of the flexible loop, shown here as a dark shaded loop.

FIGURE 15 depicts a schematic ribbon diagram of *S. cerevisiae* TIM complexed with 2-phosphoglycolytic acid (dark spheres), illustrating the "closed" conformation of the flexible loop, shown here as a dark shaded loop.

FIGURE 16 depicts a solvent accessible surface representation of the *P. aeruginosa* TIM dimer, onto which sequence conservation is mapped. The degree of variation in sequence observed among the bacterial organisms *P. aeruginosa, E. coli, S. aureus, S. pneumonia, H. pylori* and *E. faecilis* is mapped onto the *P. aeruginosa* TpiA structure. Sequence variation is illustrated by the color coding scheme: completely conserved residues are red with lighter shades of red representing progressively less conservation; white represents residues that have an average degree of sequence conservation; and blue represents residues that are more variable than average. The highly conserved region around the active site (encircled), including the "flexible loop" (arrow), can be clearly identified in this diagram. Additionally, the N-terminal end of the opposing TIM barrel in the dimer is also visible (on the right), showing that this region of the enzyme is less conserved.

FIGURE 17 contains Table 4, which lists the residues in the intersubunit region of TcTIM (*T. cruzi*), PaTIM (*P. aeruginosa*), and HsTIM (*H. sapiens*).

FIGURE 18 depicts potential druggable intersubunit residues in *P. aeruginosa* TIM (PaTIM), Cys43 and Cys88, which are depicted in green.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing.

The term "binding" refers to an association, which may be a stable association, between two molecules, e.g., between a polypeptide of the invention and a binding partner, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

A "comparison window," as used herein, refers to a conceptual segment of at least 20 contiguous amino acid positions wherein a protein sequence may be compared to a reference sequence of at least 20 contiguous amino acids and wherein the portion of the protein sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2: 482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48: 443, by the search

for similarity method of Pearson and Lipman (1988) Proc. Natl. Acad. Sci. (U.S.A.) 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods may be identified.

The term "complex" refers to an association between at least two moieties (e.g. chemical or biochemical) that have an affinity for one another. Examples of complexes include associations between antigen/antibodies, lectin/avidin, target polynucleotide/probe oligonucleotide, antibody/anti-antibody, receptor/ligand, enzyme/ligand, polypeptide/ polypeptide, polypeptide/polynucleotide, polypeptide/co-factor, polypeptide/substrate, polypeptide/inhibitor, polypeptide/small molecule, and the like. "Member of a complex" refers to one moiety of the complex, such as an antigen or ligand. "Protein complex" or "polypeptide complex" refers to a complex comprising at least one polypeptide.

The term "conserved residue" refers to an amino acid that is a member of a group of amino acids having certain common properties. The term "conservative amino acid substitution" refers to the substitution (conceptually or otherwise) of an amino acid from one such group with a different amino acid from the same group. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz, G. E. and R. H. Schirmer., Principles of Protein Structure, Springer-Verlag). According to such analyses, groups of amino acids may be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz, G. E. and R. H. Schirmer, Principles of Protein Structure, Springer-Verlag). One example of a set of amino acid groups defined in this manner include: (i) a charged group, consisting of Glu and Asp, Lys, Arg and His, (ii) a positively-charged group, consisting of Lys, Arg and His, (iii) a negatively-charged group, consisting of Glu and Asp, (iv) an aromatic group, consisting of Phe, Tyr and Trp, (v) a nitrogen ring group, consisting of His and Trp, (vi) a large aliphatic nonpolar group, consisting of Val, Leu and Ile, (vii) a slightly-polar group, consisting of Met and Cys, (viii) a small-residue group, consisting of Ser, Thr, Asp, Asn, Gly, Ala, Glu, Gln and Pro, (ix) an aliphatic group consisting of Val, Leu, Ile, Met and Cys, and (x) a small hydroxyl group consisting of Ser and Thr.

The term "domain", when used in connection with a polypeptide, refers to a specific region within such polypeptide that comprises a particular structure or mediates a particular function. In the typical case, a domain of a polypeptide of the invention is a fragment of the polypeptide. In certain instances, a domain is a structurally stable domain, as evidenced, for example, by mass spectroscopy, or by the fact that a modulator may bind to a druggable region of the domain.

The term "druggable region", when used in reference to a polypeptide, nucleic acid, complex and the like, refers to a region of the molecule which is a target or is a likely target for binding a modulator. For a polypeptide, a druggable region generally refers to a region wherein several amino acids of a polypeptide would be capable of interacting with a modulator or other molecule. For a polypeptide or complex thereof, exemplary druggable regions including binding pockets and sites, enzymatic active sites, interfaces between domains of a polypeptide or complex, surface grooves or contours or surfaces of a polypeptide or complex which are capable of participating in interactions with another molecule. In certain instances, the interacting molecule is another polypeptide, which may be naturally-occurring. In other instances, the druggable region is on the surface of the molecule.

Druggable regions may be described and characterized in a number of ways. For example, a druggable region may be characterized by some or all of the amino acids that make up the region, or the backbone atoms thereof, or the side chain atoms thereof (optionally with or without the Cα atoms). Alternatively, in certain instances, the volume of a druggable region corresponds to that of a carbon based molecule of at least about 200 amu and often up to about 800 amu. In other instances, it will be appreciated that the volume of such region may correspond to a molecule of at least about 600 amu and often up to about 1600 amu or more.

Alternatively, a druggable region may be characterized by comparison to other regions on the same or other molecules. For example, the term "affinity region" refers to a druggable region on a molecule (such as a polypeptide of the invention) that is present in several other molecules, in so much as the structures of the same affinity regions are sufficiently the same so that they are expected to bind the same or related structural analogs. An example of an affinity region is an ATP-binding site of a protein kinase that is found in several protein kinases (whether or not of the same origin). The term "selectivity

region" refers to a druggable region of a molecule that may not be found on other molecules, in so much as the structures of different selectivity regions are sufficiently different so that they are not expected to bind the same or related structural analogs. An exemplary selectivity region is a catalytic domain of a protein kinase that exhibits specificity for one substrate. In certain instances, a single modulator may bind to the same affinity region across a number of proteins that have a substantially similar biological function, whereas the same modulator may bind to only one selectivity region of one of those proteins.

Continuing with examples of different druggable regions, the term "undesired region" refers to a druggable region of a molecule that upon interacting with another molecule results in an undesirable affect. For example, a binding site that oxidizes the interacting molecule (such as P-450 activity) and thereby results in increased toxicity for the oxidized molecule may be deemed a "undesired region". Other examples of potential undesired regions includes regions that upon interaction with a drug decrease the membrane permeability of the drug, increase the excretion of the drug, or increase the blood brain transport of the drug. It may be the case that, in certain circumstances, an undesired region will be no longer be deemed an undesired region because the affect of the region will be favorable, e.g., a drug intended to treat a brain condition would benefit from interacting with a region that resulted in increased blood brain transport, whereas the same region could be deemed undesirable for drugs that were not intended to be delivered to the brain.

When used in reference to a druggable region, the "selectivity" or "specificity' of a molecule such as a modulator to a druggable region may be used to describe the binding between the molecule and a druggable region. For example, the selectivity of a modulator with respect to a druggable region may be expressed by comparison to another modulator, using the respective values of K_d (i.e., the dissociation constants for each modulator-druggable region complex) or, in cases where a biological effect is observed below the K_d, the ratio of the respective EC_{50}'s (i.e., the concentrations that produce 50% of the maximum response for the modulator interacting with each druggable region).

A "fusion protein" or "fusion polypeptide" refers to a chimeric protein as that term is known in the art and may be constructed using methods known in the art. In many examples of fusion proteins, there are two different polypeptide sequences, and in certain cases, there may be more. The sequences may be linked in frame. A fusion protein may include a domain which is found (albeit in a different protein) in an organism which also

expresses the first protein, or it may be an "interspecies", "intergenic", etc. fusion expressed by different kinds of organisms. In various embodiments, the fusion polypeptide may comprise one or more amino acid sequences linked to a first polypeptide. In the case where more than one amino acid sequence is fused to a first polypeptide, the fusion sequences may be multiple copies of the same sequence, or alternatively, may be different amino acid sequences. The fusion polypeptides may be fused to the N-terminus, the C-terminus, or the N- and C-terminus of the first polypeptide. Exemplary fusion proteins include polypeptides comprising a glutathione S-transferase tag (GST-tag), histidine tag (His-tag), an immunoglobulin domain or an immunoglobulin binding domain.

The term "gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide having exon sequences and optionally intron sequences. The term "intron" refers to a DNA sequence present in a given gene which is not translated into protein and is generally found between exons.

The term "having substantially similar biological activity", when used in reference to two polypeptides, refers to a biological activity of a first polypeptide which is substantially similar to at least one of the biological activities of a second polypeptide. A substantially similar biological activity means that the polypeptides carry out a similar function, e.g., a similar enzymatic reaction or a similar physiological process, etc. For example, two homologous proteins may have a substantially similar biological activity if they are involved in a similar enzymatic reaction, e.g., they are both kinases which catalyze phosphorylation of a substrate polypeptide, however, they may phosphorylate different regions on the same protein substrate or different substrate proteins altogether. Alternatively, two homologous proteins may also have a substantially similar biological activity if they are both involved in a similar physiological process, e.g., transcription. For example, two proteins may be transcription factors, however, they may bind to different DNA sequences or bind to different polypeptide interactors. Substantially similar biological activities may also be associated with proteins carrying out a similar structural role, for example, two membrane proteins.

The term "isolated polypeptide" refers to a polypeptide, in certain embodiments prepared from recombinant DNA or RNA, or of synthetic origin, or some combination thereof, which (1) is not associated with proteins that it is normally found with in nature, (2) is isolated from the cell in which it normally occurs, (3) is isolated free of other proteins

from the same cellular source, e.g. free of *P. aeruginosa* proteins, (4) is expressed by a cell from a different species, or (5) does not occur in nature.

The term "isolated nucleic acid" refers to a polynucleotide of genomic, cDNA, or synthetic origin or some combination there of, which (1) is not associated with the cell in which the "isolated nucleic acid" is found in nature, or (2) is operably linked to a polynucleotide to which it is not linked in nature.

The terms "label" or "labeled" refer to incorporation or attachment, optionally covalently or non-covalently, of a detectable marker into a molecule, such as a polypeptide. Various methods of labeling polypeptides are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes, fluorescent labels, heavy atoms, enzymatic labels or reporter genes, chemiluminescent groups, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). Examples and use of such labels are described in more detail below. In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

The term "modulation", when used in reference to a functional property or biological activity or process (e.g., enzyme activity or receptor binding), refers to the capacity to either up regulate (e.g., activate or stimulate), down regulate (e.g., inhibit or suppress) or otherwise change a quality of such property, activity or process. In certain instances, such regulation may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types.

The term "modulator" refers to a polypeptide, nucleic acid, macromolecule, complex, molecule, small molecule, compound, species or the like (naturally-occurring or non-naturally-occurring), or an extract made from biological materials such as bacteria, plants, fungi, or animal cells or tissues, that may be capable of causing modulation. Modulators may be evaluated for potential activity as inhibitors or activators (directly or indirectly) of a functional property, biological activity or process, or combination of them, (e.g., agonist, partial antagonist, partial agonist, inverse agonist, antagonist, anti-microbial

agents, inhibitors of microbial infection or proliferation, and the like) by inclusion in assays. In such assays, many modulators may be screened at one time. The activity of a modulator may be known, unknown or partially known.

The term "motif" refers to an amino acid sequence that is commonly found in a protein of a particular structure or function. Typically, a consensus sequence is defined to represent a particular motif. The consensus sequence need not be strictly defined and may contain positions of variability, degeneracy, variability of length, etc. The consensus sequence may be used to search a database to identify other proteins that may have a similar structure or function due to the presence of the motif in its amino acid sequence. For example, on-line databases may be searched with a consensus sequence in order to identify other proteins containing a particular motif. Various search algorithms and/or programs may be used, including FASTA, BLAST or ENTREZ. FASTA and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.). ENTREZ is available through the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD.

The term "naturally-occurring", as applied to an object, refers to the fact that an object may be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including bacteria) that may be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The term "nucleic acid" refers to a polymeric form of nucleotides, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The terms should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides.

The term "nucleic acid of the invention" refers to a nucleic acid encoding a polypeptide of the invention, e.g., a nucleic acid comprising a sequence consisting of, or consisting essentially of, the polynucleotide sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3. A nucleic acid of the invention may comprise all, or a portion of: the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID

NO: 3; nucleotide sequences encoding polypeptides that are functionally equivalent to polypeptides of the invention; nucleotide sequences encoding polypeptides at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% homologous or identical with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences encoding polypeptides having an activity of a polypeptide of the invention and having at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% or more homology or identity with SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences that differ by 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more nucleotide substitutions, additions or deletions, such as allelic variants, of SEQ ID NO: 1 and SEQ ID NO: 3; nucleic acids derived from and evolutionarily related to SEQ ID NO: 1 or SEQ ID NO: 3; and complements of, and nucleotide sequences resulting from the degeneracy of the genetic code, for all of the foregoing and other nucleic acids of the invention. Nucleic acids of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 1 or SEQ ID NO: 3 and also variants of SEQ ID NO: 1 or SEQ ID NO: 3 which have been codon optimized for expression in a particular organism (e.g., host cell).

The term "operably linked", when describing the relationship between two nucleic acid regions, refers to a juxtaposition wherein the regions are in a relationship permitting them to function in their intended manner. For example, a control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences, such as when the appropriate molecules (e.g., inducers and polymerases) are bound to the control or regulatory sequence(s).

The term "phenotype" refers to the entire physical, biochemical, and physiological makeup of a cell, e.g., having any one trait or any group of traits.

The term "polypeptide", and the terms "protein" and "peptide" which are used interchangeably herein, refers to a polymer of amino acids. Exemplary polypeptides include gene products, naturally-occurring proteins, homologs, orthologs, paralogs, fragments, and other equivalents, variants and analogs of the foregoing.

The terms "polypeptide fragment" or "fragment", when used in reference to a reference polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical to the corresponding positions in the reference polypeptide. Such

deletions may occur at the amino-terminus or carboxy-terminus of the reference polypeptide, or alternatively both. Fragments typically are at least 5, 6, 8 or 10 amino acids long, at least 14 amino acids long, at least 20, 30, 40 or 50 amino acids long, at least 75 amino acids long, or at least 100, 150, 200, 300, 500 or more amino acids long. A fragment can retain one or more of the biological activities of the reference polypeptide. In certain embodiments, a fragment may comprise a druggable region, and optionally additional amino acids on one or both sides of the druggable region, which additional amino acids may number from 5, 10, 15, 20, 30, 40, 50, or up to 100 or more residues. Further, fragments can include a sub-fragment of a specific region, which sub-fragment retains the function of the region from which it is derived. In another embodiment, a fragment may have immunogenic properties.

The term "polypeptide of the invention" refers to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or an equivalent or fragment thereof, e.g., a polypeptide comprising a sequence consisting of, or consisting essentially of, the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4. Polypeptides of the invention include polypeptides comprising all or a portion of the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more conservative amino acid substitutions; an amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2 or SEQ ID NO: 4; and functional fragments thereof. Polypeptides of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 2 or SEQ ID NO: 4.

The term "purified" refers to an object species that is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). A "purified fraction" is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all species present. In making the determination of the purity of a species in solution or dispersion, the solvent or matrix in which the species is dissolved or dispersed is usually not included in such determination; instead, only the species (including the one of interest) dissolved or dispersed are taken into account. Generally, a purified composition will have one species that comprises more than about 80 percent of all species present in the composition, more than about 85%, 90%, 95%, 99% or more of all species present. The object species may be purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional

detection methods) wherein the composition consists essentially of a single species. A skilled artisan may purify a polypeptide of the invention using standard techniques for protein purification in light of the teachings herein. Purity of a polypeptide may be determined by a number of methods known to those of skill in the art, including for example, amino-terminal amino acid sequence analysis, gel electrophoresis, mass-spectrometry analysis and the methods described in the Exemplification section herein.

The terms "recombinant protein" or "recombinant polypeptide" refer to a polypeptide which is produced by recombinant DNA techniques. An example of such techniques includes the case when DNA encoding the expressed protein is inserted into a suitable expression vector which is in turn used to transform a host cell to produce the protein or polypeptide encoded by the DNA.

A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length protein given in a sequence listing such as SEQ ID NO: 2 or SEQ ID NO: 4, or may comprise a complete protein sequence. Generally, a reference sequence is at least 200, 300 or 400 nucleotides in length, frequently at least 600 nucleotides in length, and often at least 800 nucleotides in length (or the protein equivalent if it is shorter or longer in length). Because two proteins may each (1) comprise a sequence (i.e., a portion of the complete protein sequence) that is similar between the two proteins, and (2) may further comprise a sequence that is divergent between the two proteins, sequence comparisons between two (or more) proteins are typically performed by comparing sequences of the two proteins over a "comparison window" to identify and compare local regions of sequence similarity.

The term "regulatory sequence" is a generic term used throughout the specification to refer to polynucleotide sequences, such as initiation signals, enhancers, regulators and promoters, that are necessary or desirable to affect the expression of coding and non-coding sequences to which they are operably linked. Exemplary regulatory sequences are described in Goeddel; *Gene Expression Technology: Methods in Enzymology*, Academic Press, San Diego, CA (1990), and include, for example, the early and late promoters of SV40, adenovirus or cytomegalovirus immediate early promoter, the lac system, the trp system, the TAC or TRC system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda, the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes,

the promoters of acid phosphatase, e.g., Pho5, the promoters of the yeast α-mating factors, the polyhedron promoter of the baculovirus system and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. The nature and use of such control sequences may differ depending upon the host organism. In prokaryotes, such regulatory sequences generally include promoter, ribosomal binding site, and transcription termination sequences. The term "regulatory sequence" is intended to include, at a minimum, components whose presence may influence expression, and may also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. In certain embodiments, transcription of a polynucleotide sequence is under the control of a promoter sequence (or other regulatory sequence) which controls the expression of the polynucleotide in a cell-type in which expression is intended. It will also be understood that the polynucleotide can be under the control of regulatory sequences which are the same or different from those sequences which control expression of the naturally-occurring form of the polynucleotide.

The term "reporter gene" refers to a nucleic acid comprising a nucleotide sequence encoding a protein that is readily detectable either by its presence or activity, including, but not limited to, luciferase, fluorescent protein (e.g., green fluorescent protein), chloramphenicol acetyl transferase, β-galactosidase, secreted placental alkaline phosphatase, β-lactamase, human growth hormone, and other secreted enzyme reporters. Generally, a reporter gene encodes a polypeptide not otherwise produced by the host cell, which is detectable by analysis of the cell(s), e.g., by the direct fluorometric, radioisotopic or spectrophotometric analysis of the cell(s) and preferably without the need to kill the cells for signal analysis. In certain instances, a reporter gene encodes an enzyme, which produces a change in fluorometric properties of the host cell, which is detectable by qualitative, quantitative or semiquantitative function or transcriptional activation. Exemplary enzymes include esterases, β-lactamase, phosphatases, peroxidases, proteases (tissue plasminogen activator or urokinase) and other enzymes whose function may be detected by appropriate chromogenic or fluorogenic substrates known to those skilled in the art or developed in the future.

The term "sequence homology" refers to the proportion of base matches between two nucleic acid sequences or the proportion of amino acid matches between two amino acid sequences. When sequence homology is expressed as a percentage, e.g., 50%, the

percentage denotes the proportion of matches over the length of sequence from a desired sequence (e.g., SEQ. ID NO: 1) that is compared to some other sequence. Gaps (in either of the two sequences) are permitted to maximize matching; gap lengths of 15 bases or less are usually used, 6 bases or less are used more frequently, with 2 bases or less used even more frequently. The term "sequence identity" means that sequences are identical (i.e., on a nucleotide-by-nucleotide basis for nucleic acids or amino acid-by-amino acid basis for polypeptides) over a window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the comparison window, determining the number of positions at which the identical amino acids occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the comparison window, and multiplying the result by 100 to yield the percentage of sequence identity. Methods to calculate sequence identity are known to those of skill in the art and described in further detail below.

The term "small molecule" refers to a compound, which has a molecular weight of less than about 5 kD, less than about 2.5 kD, less than about 1.5 kD, or less than about 0.9 kD. Small molecules may be, for example, nucleic acids, peptides, polypeptides, peptide nucleic acids, peptidomimetics, carbohydrates, lipids or other organic (carbon containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention. The term "small organic molecule" refers to a small molecule that is often identified as being an organic or medicinal compound, and does not include molecules that are exclusively nucleic acids, peptides or polypeptides.

The term "soluble" as used herein with reference to a polypeptide of the invention or other protein, means that upon expression in cell culture, at least some portion of the polypeptide or protein expressed remains in the cytoplasmic fraction of the cell and does not fractionate with the cellular debris upon lysis and centrifugation of the lysate. Solubility of a polypeptide may be increased by a variety of art recognized methods, including fusion to a heterologous amino acid sequence, deletion of amino acid residues, amino acid substitution (e.g., enriching the sequence with amino acid residues having hydrophilic side chains), and chemical modification (e.g., addition of hydrophilic groups). The solubility of polypeptides may be measured using a variety of art recognized techniques, including, dynamic light scattering to determine aggregation state, UV absorption, centrifugation to separate aggregated from non-aggregated material, and SDS

gel electrophoresis (e.g., the amount of protein in the soluble fraction is compared to the amount of protein in the soluble and insoluble fractions combined). When expressed in a host cell, the polypeptides of the invention may be at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more soluble, e.g., at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the total amount of protein expressed in the cell is found in the cytoplasmic fraction. In certain embodiments, a one liter culture of cells expressing a polypeptide of the invention will produce at least about 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30, 40, 50 milligrams or more of soluble protein. In an exemplary embodiment, a polypeptide of the invention is at least about 10% soluble and will produce at least about 1 milligram of protein from a one liter cell culture.

The term "specifically hybridizes" refers to detectable and specific nucleic acid binding. Polynucleotides, oligonucleotides and nucleic acids of the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. Stringent conditions may be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and nucleic acids of the invention and a nucleic acid sequence of interest will be at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99%, or more. In certain instances, hybridization and washing conditions are performed at under stringent conditions according to conventional hybridization procedures and as described further herein.

The terms "stringent conditions" or "stringent hybridization conditions" refer to conditions which promote specific hydribization between two complementary polynucleotide strands so as to form a duplex. Stringent conditions may be selected to be about 5°C lower than the thermal melting point (Tm) for a given polynucleotide duplex at a defined ionic strength and pH. The length of the complementary polynucleotide strands and their GC content will determine the Tm of the duplex, and thus the hybridization conditions necessary for obtaining a desired specificity of hybridization. The Tm is the temperature (under defined ionic strength and pH) at which 50% of the a polynucleotide sequence hybridizes to a perfectly matched complementary strand. In certain cases it may be desirable to increase the stringency of the hybridization conditions to be about equal to the Tm for a particular duplex.

A variety of techniques for estimating the Tm are available. Typically, G-C base pairs in a duplex are estimated to contribute about 3°C to the Tm, while A-T base pairs are estimated to contribute about 2°C, up to a theoretical maximum of about 80-100°C. However, more sophisticated models of Tm are available in which G-C stacking interactions, solvent effects, the desired assay temperature and the like are taken into account. For example, probes can be designed to have a dissociation temperature (Td) of approximately 60°C, using the formula: Td = (((((3 x #GC) + (2 x #AT)) x 37) - 562)/#bp) - 5; where #GC, #AT, and #bp are the number of guanine-cytosine base pairs, the number of adenine-thymine base pairs, and the number of total base pairs, respectively, involved in the formation of the duplex.

Hybridization may be carried out in 5xSSC, 4xSSC, 3xSSC, 2xSSC, 1xSSC or 0.2xSSC for at least about 1 hour, 2 hours, 5 hours, 12 hours, or 24 hours. The temperature of the hybridization may be increased to adjust the stringency of the reaction, for example, from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, or 65°C. The hybridization reaction may also include another agent affecting the stringency, for example, hybridization conducted in the presence of 50% formamide increases the stringency of hybridization at a defined temperature.

The hybridization reaction may be followed by a single wash step, or two or more wash steps, which may be at the same or a different salinity and temperature. For example, the temperature of the wash may be increased to adjust the stringency from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, 65°C, or higher. The wash step may be conducted in the presence of a detergent, e.g., 0.1 or 0.2% SDS. For example, hybridization may be followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and optionally two additional wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Exemplary stringent hybridization conditions include overnight hybridization at 65°C in a solution comprising, or consisting of, 50% formamide, 10xDenhardt (0.2% Ficoll, 0.2% Polyvinylpyrrolidone, 0.2% bovine serum albumin) and 200 μg/ml of denatured carrier DNA, e.g., sheared salmon sperm DNA, followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and two wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Hybridization may consist of hybridizing two nucleic acids in solution, or a nucleic acid in solution to a nucleic acid attached to a solid support, e.g., a filter. When one nucleic

acid is on a solid support, a prehybridization step may be conducted prior to hybridization. Prehybridization may be carried out for at least about 1 hour, 3 hours or 10 hours in the same solution and at the same temperature as the hybridization solution (without the complementary polynucleotide strand).

Appropriate stringency conditions are known to those skilled in the art or may be determined experimentally by the skilled artisan. See, for example, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6; Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, N.Y; S. Agrawal (ed.) Methods in Molecular Biology, volume 20; Tijssen (1993) Laboratory Techniques in biochemistry and molecular biology-hybridization with nucleic acid probes, e.g., part I chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, New York; and Tibanyenda, N. et al., Eur. J. Biochem. 139:19 (1984) and Ebel, S. et al., Biochem. 31:12083 (1992).

As applied to proteins, the term "substantial identity" means that two protein sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, typically share at least about 70 percent sequence identity, alternatively at least about 80, 85, 90, 95 percent sequence identity or more. In certain instances, residue positions that are not identical differ by conservative amino acid substitutions, which are described above.

The term "structural motif", when used in reference to a polypeptide, refers to a polypeptide that, although it may have different amino acid sequences, may result in a similar structure, wherein by structure is meant that the motif forms generally the same tertiary structure, or that certain amino acid residues within the motif, or alternatively their backbone or side chains (which may or may not include the Cα atoms of the side chains) are positioned in a like relationship with respect to one another in the motif.

The term "test compound" refers to a molecule to be tested by one or more screening method(s) as a putative modulator of a polypeptide of the invention or other biological entity or process. A test compound is usually not known to bind to a target of interest. The term "control test compound" refers to a compound known to bind to the target (e.g., a known agonist, antagonist, partial agonist or inverse agonist). The term "test compound" does not include a chemical added as a control condition that alters the function of the target to determine signal specificity in an assay. Such control chemicals or conditions include chemicals that 1) nonspecifically or substantially disrupt protein

structure (e.g., denaturing agents (e.g., urea or guanidinium), chaotropic agents, sulfhydryl reagents (e.g., dithiothreitol and β-mercaptoethanol), and proteases), 2) generally inhibit cell metabolism (e.g., mitochondrial uncouplers) and 3) non-specifically disrupt electrostatic or hydrophobic interactions of a protein (e.g., high salt concentrations, or detergents at concentrations sufficient to non-specifically disrupt hydrophobic interactions). Further, the term "test compound" also does not include compounds known to be unsuitable for a therapeutic use for a particular indication due to toxicity of the subject. In certain embodiments, various predetermined concentrations of test compounds are used for screening such as 0.01 μM, 0.1 μM, 1.0 μM, and 10.0 μM. Examples of test compounds include, but are not limited to, peptides, nucleic acids, carbohydrates, and small molecules. The term "novel test compound" refers to a test compound that is not in existence as of the filing date of this application. In certain assays using novel test compounds, the novel test compounds comprise at least about 50%, 75%, 85%, 90%, 95% or more of the test compounds used in the assay or in any particular trial of the assay.

The term "therapeutically effective amount" refers to that amount of a modulator, drug or other molecule which is sufficient to effect treatment when administered to a subject in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "transfection" means the introduction of a nucleic acid, e.g., an expression vector, into a recipient cell, which in certain instances involves nucleic acid-mediated gene transfer. The term "transformation" refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous nucleic acid. For example, a transformed cell may express a recombinant form of a polypeptide of the invention or antisense expression may occur from the transferred gene so that the expression of a naturally-occurring form of the gene is disrupted.

The term "transgene" means a nucleic acid sequence, which is partly or entirely heterologous to a transgenic animal or cell into which it is introduced, or, is homologous to an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted (e.g., it is inserted at a location which differs

from that of the natural gene or its insertion results in a knockout). A transgene may include one or more regulatory sequences and any other nucleic acids, such as introns, that may be necessary for optimal expression.

The term "transgenic animal" refers to any animal, for example, a mouse, rat or other non-human mammal, a bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or it may be extrachromosomally replicating DNA. In the typical transgenic animals described herein, the transgene causes cells to express a recombinant form of a protein. However, transgenic animals in which the recombinant gene is silent are also contemplated.

The term "vector" refers to a nucleic acid capable of transporting another nucleic acid to which it has been linked. One type of vector which may be used in accord with the invention is an episome, i.e., a nucleic acid capable of extra-chromosomal replication. Other vectors include those capable of autonomous replication and expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer to circular double stranded DNA molecules which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

2. Polypeptides of the Invention

The present invention makes available in a variety of embodiments soluble, purified and/or isolated forms of the polypeptides of the invention. Milligram quantities of an exemplary polypeptide of the invention, SEQ ID NO: 4 (optionally with a tag, and optionally labeled), have been isolated in a highly purified form. The present invention provides for expressing and purifying polypeptides of the invention in quantities that equal or exceed the quantity of polypeptide(s) of the invention expressed and purified as provided in the Exemplification section below (or smaller amount(s) thereof, such as 25%, 33%, 50% or 75% of the amount(s) so expressed and/or purified).

In one aspect, the present invention contemplates an isolated polypeptide comprising (a) the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, (b) the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 20 conservative amino acid substitutions, deletions or additions, (c) an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 4 or (d) a functional fragment of a polypeptide having an amino acid sequence set forth in (a), (b) or (c). In another aspect, the present invention contemplates a composition comprising such an isolated polypeptide and less than about 10%, or alternatively 5%, or alternatively 1%, contaminating biological macromolecules or polypeptides.

It may be the case that the amino acid sequence of SEQ ID NO: 4 differs from that of SEQ ID NO: 2 by one or more amino acids. SEQ ID NO: 4 is determined from the experimentally determined nucleic acid sequence SED ID NO: 3, and SEQ ID NO: 2 is determined from SEQ ID NO: 1, which is obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, and variants thereof, as well as any differences (if any) in the polypeptides of the invention based on those SEQ ID NOS and nucleic acid sequences encoding the same.

In certain embodiments, a polypeptide of the invention is a fusion protein containing a domain which increases its solubility and/or facilitates its purification, identification, detection, and/or structural characterization. Exemplary domains, include, for example, glutathione S-transferase (GST), protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose binding protein, HA, myc, poly arginine, poly His, poly His-Asp or

FLAG fusion proteins and tags. Additional exemplary domains include domains that alter protein localization *in vivo*, such as signal peptides, type III secretion system-targeting peptides, transcytosis domains, nuclear localization signals, etc. In various embodiments, a polypeptide of the invention may comprise one or more heterologous fusions. Polypeptides may contain multiple copies of the same fusion domain or may contain fusions to two or more different domains. The fusions may occur at the N-terminus of the polypeptide, at the C-terminus of the polypeptide, or at both the N- and C-terminus of the polypeptide. It is also within the scope of the invention to include linker sequences between a polypeptide of the invention and the fusion domain in order to facilitate construction of the fusion protein or to optimize protein expression or structural constraints of the fusion protein. In another embodiment, the polypeptide may be constructed so as to contain protease cleavage sites between the fusion polypeptide and polypeptide of the invention in order to remove the tag after protein expression or thereafter. Examples of suitable endoproteases, include, for example, Factor Xa and TEV proteases.

In another embodiment, a polypeptide of the invention may be modified so that its rate of traversing the cellular membrane is increased. For example, the polypeptide may be fused to a second peptide which promotes "transcytosis," e.g., uptake of the peptide by cells. The peptide may be a portion of the HIV transactivator (TAT) protein, such as the fragment corresponding to residues 37 -62 or 48-60 of TAT, portions which have been observed to be rapidly taken up by a cell *in vitro* (Green and Loewenstein, (1989) Cell 55:1179-1188). Alternatively, the internalizing peptide may be derived from the *Drosophila antennapedia* protein, or homologs thereof. The 60 amino acid long homeodomain of the homeo-protein antennapedia has been demonstrated to translocate through biological membranes and can facilitate the translocation of heterologous polypeptides to which it is coupled. Thus, polypeptides may be fused to a peptide consisting of about amino acids 42-58 of *Drosophila antennapedia* or shorter fragments for transcytosis (Derossi et al. (1996) J Biol Chem 271:18188-18193; Derossi et al. (1994) J Biol Chem 269:10444-10450; and Perez et al. (1992) J Cell Sci 102:717-722). The transcytosis polypeptide may also be a non-naturally-occurring membrane-translocating sequence (MTS), such as the peptide sequences disclosed in U.S. Patent No. 6,248,558.

In another embodiment, a polypeptide of the invention is labeled with an isotopic label to facilitate its detection and or structural characterization using nuclear magnetic resonance or another applicable technique. Exemplary isotopic labels include radioisotopic

labels such as, for example, potassium-40 (^{40}K), carbon-14 (^{14}C), tritium (^{3}H), sulphur-35 (^{35}S), phosphorus-32 (^{32}P), technetium-99m (^{99m}Tc), thallium-201 (^{201}Tl), gallium-67 (^{67}Ga), indium-111 (^{111}In), iodine-123 (^{123}I), iodine-131 (^{131}I), yttrium-90 (^{90}Y), samarium-153 (^{153}Sm), rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), dysprosium-165 (^{165}Dy) and holmium-166 (^{166}Ho). The isotopic label may also be an atom with non zero nuclear spin, including, for example, hydrogen-1 (^{1}H), hydrogen-2 (^{2}H), hydrogen-3 (^{3}H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F). In certain embodiments, the polypeptide is uniformly labeled with an isotopic label, for example, wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the possible labels in the polypeptide are labeled, e.g., wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the nitrogen atoms in the polypeptide are ^{15}N, and/or wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the carbon atoms in the polypeptide are ^{13}C, and/or wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the hydrogen atoms in the polypeptide are ^{2}H. In other embodiments, the isotopic label is located in one or more specific locations within the polypeptide, for example, the label may be specifically incorporated into one or more of the leucine residues of the polypeptide. The invention also encompasses the embodiment wherein a single polypeptide comprises two, three or more different isotopic labels, for example, the polypeptide comprises both ^{15}N and ^{13}C labeling.

In yet another embodiment, the polypeptides of the invention are labeled to facilitate structural characterization using x-ray crystallography or another applicable technique. Exemplary labels include heavy atom labels such as, for example, cobalt, selenium, krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium. In an exemplary embodiment, the polypeptide is labeled with seleno-methionine.

A variety of methods are available for preparing a polypeptide with a label, such as a radioisotopic label or heavy atom label. For example, in one such method, an expression vector comprising a nucleic acid encoding a polypeptide is introduced into a host cell, and the host cell is cultured in a cell culture medium in the presence of a source of the label, thereby generating a labeled polypeptide. As indicated above, the extent to which a polypeptide may be labeled may vary.

In still another embodiment, the polypeptides of the invention are labeled with a fluorescent label to facilitate their detection, purification, or structural characterization. In an exemplary embodiment, a polypeptide of the invention is fused to a heterologous polypeptide sequence which produces a detectable fluorescent signal, including, for example, green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), Renilla Reniformis green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, microtiter plates, slides, beads, films, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array of *P. aeruginosa* polypeptide sequences.

In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array that contains at least some polypeptide sequences from *P. aeruginosa*.

In still other embodiments, the invention comprises the polypeptide sequences of the invention in computer readable format. The invention also encompasses a database comprising the polypeptide sequences of the invention.

In other embodiments, the invention relates to the polypeptides of the invention contained within a vessels useful for manipulation of the polypeptide sample. For example, the polypeptides of the invention may be contained within a microtiter plate to facilitate detection, screening or purification of the polypeptide. The polypeptides may also be contained within a syringe as a container suitable for administering the polypeptide to a subject in order to generate antibodies or as part of a vaccination regimen. The

polypeptides may also be contained within an NMR tube in order to enable characterization by nuclear magnetic resonance techniques.

In still other embodiments, the invention relates to a crystallized polypeptide of the invention and crystallized polypeptides which have been mounted for examination by x-ray crystallography as described further below. In certain instances, a polypeptide of the invention in crystal form may be single crystals of various dimensions (e.g., micro-crystals) or may be an aggregate of crystalline material. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and one or more of the following: a co-factor (such as a salt, metal, nucleotide, oligonucleotide or polypeptide), a modulator, or a small molecule. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and any other molecule or atom (such as a metal ion) that associates with the polypeptide *in vivo*.

In certain embodiments, polypeptides of the invention may be synthesized chemically, ribosomally in a cell free system, or ribosomally within a cell. Chemical synthesis of polypeptides of the invention may be carried out using a variety of art recognized methods, including stepwise solid phase synthesis, semi-synthesis through the conformationally-assisted re-ligation of peptide fragments, enzymatic ligation of cloned or synthetic peptide segments, and chemical ligation. Native chemical ligation employs a chemoselective reaction of two unprotected peptide segments to produce a transient thioester-linked intermediate. The transient thioester-linked intermediate then spontaneously undergoes a rearrangement to provide the full length ligation product having a native peptide bond at the ligation site. Full length ligation products are chemically identical to proteins produced by cell free synthesis. Full length ligation products may be refolded and/or oxidized, as allowed, to form native disulfide-containing protein molecules. (see e.g., U.S. Patent Nos. 6,184,344 and 6,174,530; and T. W. Muir et al., Curr. Opin. Biotech. (1993): vol. 4, p 420; M. Miller, et al., Science (1989): vol. 246, p 1149; A. Wlodawer, et al., Science (1989): vol. 245, p 616; L. H. Huang, et al., Biochemistry (1991): vol. 30, p 7402; M. Schnolzer, et al., Int. J. Pept. Prot. Res. (1992): vol. 40, p 180-193; K. Rajarathnam, et al., Science (1994): vol. 264, p 90; R. E. Offord, "Chemical Approaches to Protein Engineering", in Protein Design and the Development of New therapeutics and Vaccines, J. B. Hook, G. Poste, Eds., (Plenum Press, New York, 1990) pp. 253-282; C. J. A. Wallace, et al., J. Biol. Chem. (1992): vol. 267, p 3852; L. Abrahmsen, et al., Biochemistry (1991): vol. 30, p 4151; T. K. Chang, et al., Proc. Natl. Acad. Sci. USA

(1994) 91: 12544-12548; M. Schnlzer, et al., Science (1992): vol., 3256, p 221; and K. Akaji, et al., Chem. Pharm. Bull. (Tokyo) (1985) 33: 184).

In certain embodiments, it may be advantageous to provide naturally-occurring or experimentally-derived homologs of a polypeptide of the invention. Such homologs may function in a limited capacity as a modulator to promote or inhibit a subset of the biological activities of the naturally-occurring form of the polypeptide. Thus, specific biological effects may be elicited by treatment with a homolog of limited function, and with fewer side effects relative to treatment with agonists or antagonists which are directed to all of the biological activities of a polypeptide of the invention. For instance, antagonistic homologs may be generated which interfere with the ability of the wild-type polypeptide of the invention to associate with certain proteins, but which do not substantially interfere with the formation of complexes between the native polypeptide and other cellular proteins.

Another aspect of the invention relates to polypeptides derived from the full-length polypeptides of the invention. Isolated peptidyl portions of those polypeptides may be obtained by screening polypeptides recombinantly produced from the corresponding fragment of the nucleic acid encoding such polypeptides. In addition, fragments may be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. For example, proteins may be arbitrarily divided into fragments of desired length with no overlap of the fragments, or may be divided into overlapping fragments of a desired length. The fragments may be produced (recombinantly or by chemical synthesis) and tested to identify those peptidyl fragments having a desired property, for example, the capability of functioning as a modulator of the polypeptides of the invention. In an illustrative embodiment, peptidyl portions of a protein of the invention may be tested for binding activity, as well as inhibitory ability, by expression as, for example, thioredoxin fusion proteins, each of which contains a discrete fragment of a protein of the invention (see, for example, U.S. Patents 5,270,181 and 5,292,646; and PCT publication WO94/ 02502).

In another embodiment, truncated polypeptides may be prepared. Truncated polypeptides have from 1 to 20 or more amino acid residues removed from either or both the N- and C-termini. Such truncated polypeptides may prove more amenable to expression, purification or characterization than the full-length polypeptide. For example, truncated polypeptides may prove more amenable than the full-length polypeptide to crystallization, to yielding high quality diffracting crystals or to yielding an HSQC

spectrum with high intensity peaks and minimally overlapping peaks. In addition, the use of truncated polypeptides may also identify stable and active domains of the full-length polypeptide that may be more amenable to characterization.

It is also possible to modify the structure of the polypeptides of the invention for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., *ex vivo* shelf life, resistance to proteolytic degradation *in vivo*, etc.). Such modified polypeptides, when designed to retain at least one activity of the naturally-occurring form of the protein, are considered "functional equivalents" of the polypeptides described in more detail herein. Such modified polypeptides may be produced, for instance, by amino acid substitution, deletion, or addition, which substitutions may consist in whole or part by conservative amino acid substitutions.

For instance, it is reasonable to expect that an isolated conservative amino acid substitution, such as replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, will not have a major affect on the biological activity of the resulting molecule. Whether a change in the amino acid sequence of a polypeptide results in a functional homolog may be readily determined by assessing the ability of the variant polypeptide to produce a response similar to that of the wild-type protein. Polypeptides in which more than one replacement has taken place may readily be tested in the same manner.

This invention further contemplates a method of generating sets of combinatorial mutants of polypeptides of the invention, as well as truncation mutants, and is especially useful for identifying potential variant sequences (e.g. homologs). The purpose of screening such combinatorial libraries is to generate, for example, homologs which may modulate the activity of a polypeptide of the invention, or alternatively, which possess novel activities altogether. Combinatorially-derived homologs may be generated which have a selective potency relative to a naturally-occurring protein. Such homologs may be used in the development of therapeutics.

Likewise, mutagenesis may give rise to homologs which have intracellular half-lives dramatically different than the corresponding wild-type protein. For example, the altered protein may be rendered either more stable or less stable to proteolytic degradation or other cellular process which result in destruction of, or otherwise inactivation of the protein. Such homologs, and the genes which encode them, may be utilized to alter protein

expression by modulating the half-life of the protein. As above, such proteins may be used for the development of therapeutics or treatment.

In similar fashion, protein homologs may be generated by the present combinatorial approach to act as antagonists, in that they are able to interfere with the activity of the corresponding wild-type protein.

In a representative embodiment of this method, the amino acid sequences for a population of protein homologs are aligned, preferably to promote the highest homology possible. Such a population of variants may include, for example, homologs from one or more species, or homologs from the same species but which differ due to mutation. Amino acids which appear at each position of the aligned sequences are selected to create a degenerate set of combinatorial sequences. In certain embodiments, the combinatorial library is produced by way of a degenerate library of genes encoding a library of polypeptides which each include at least a portion of potential protein sequences. For instance, a mixture of synthetic oligonucleotides may be enzymatically ligated into gene sequences such that the degenerate set of potential nucleotide sequences are expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g. for phage display).

There are many ways by which the library of potential homologs may be generated from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence may be carried out in an automatic DNA synthesizer, and the synthetic genes may then be ligated into an appropriate vector for expression. One purpose of a degenerate set of genes is to provide, in one mixture, all of the sequences encoding the desired set of potential protein sequences. The synthesis of degenerate oligonucleotides is well known in the art (see for example, Narang, SA (1983) *Tetrahedron* 39:3; Itakura et al., (1981) *Recombinant DNA, Proc.* 3rd Cleveland Sympos. Macromolecules, ed. AG Walton, Amsterdam: Elsevier pp. 273-289; Itakura et al., (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al., (1984) *Science* 198:1056; Ike et al., (1983) *Nucleic Acid Res.* 11:477). Such techniques have been employed in the directed evolution of other proteins (see, for example, Scott et al., (1990) *Science* 249:386-390; Roberts et al., (1992) *PNAS USA* 89:2429-2433; Devlin et al., (1990) *Science* 249: 404-406; Cwirla et al., (1990) *PNAS USA* 87: 6378-6382; as well as U.S. Patent Nos: 5,223,409, 5,198,346, and 5,096,815).

Alternatively, other forms of mutagenesis may be utilized to generate a combinatorial library. For example, protein homologs (both agonist and antagonist forms) may be generated and isolated from a library by screening using, for example, alanine scanning mutagenesis and the like (Ruf et al., (1994) *Biochemistry* 33:1565-1572; Wang et al., (1994) *J. Biol. Chem.* 269:3095-3099; Balint et al., (1993) *Gene* 137:109-118; Grodberg et al., (1993) *Eur. J. Biochem.* 218:597-601; Nagashima et al., (1993) *J. Biol. Chem.* 268:2888-2892; Lowman et al., (1991) *Biochemistry* 30:10832-10838; and Cunningham et al., (1989) *Science* 244:1081-1085), by linker scanning mutagenesis (Gustin et al., (1993) *Virology* 193:653-660; Brown et al., (1992) *Mol. Cell Biol.* 12:2644-2652; McKnight et al., (1982) *Science* 232:316); by saturation mutagenesis (Meyers et al., (1986) *Science* 232:613); by PCR mutagenesis (Leung et al., (1989) *Method Cell Mol Biol* 1:11-19); or by random mutagenesis (Miller et al., (1992) A Short Course in Bacterial Genetics, CSHL Press, Cold Spring Harbor, NY; and Greener et al., (1994) *Strategies in Mol Biol* 7:32-34). Linker scanning mutagenesis, particularly in a combinatorial setting, is an attractive method for identifying truncated (bioactive) forms of proteins.

A wide range of techniques are known in the art for screening gene products of combinatorial libraries made by point mutations and truncations, and for screening cDNA libraries for gene products having a certain property. Such techniques will be generally adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of protein homologs. The most widely used techniques for screening large gene libraries typically comprises cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates relatively easy isolation of the vector encoding the gene whose product was detected. Each of the illustrative assays described below are amenable to high throughput analysis as necessary to screen large numbers of degenerate sequences created by combinatorial mutagenesis techniques.

In an illustrative embodiment of a screening assay, candidate combinatorial gene products are displayed on the surface of a cell and the ability of particular cells or viral particles to bind to the combinatorial gene product is detected in a "panning assay". For instance, the gene library may be cloned into the gene for a surface membrane protein of a bacterial cell (Ladner et al., WO 88/06630; Fuchs et al., (1991) *Bio/Technology* 9:1370-1371; and Goward et al., (1992) *TIBS* 18:136-140), and the resulting fusion protein detected

by panning, e.g. using a fluorescently labeled molecule which binds the cell surface protein, e.g. FITC-substrate, to score for potentially functional homologs. Cells may be visually inspected and separated under a fluorescence microscope, or, when the morphology of the cell permits, separated by a fluorescence-activated cell sorter. This method may be used to identify substrates or other polypeptides that can interact with a polypeptide of the invention.

In similar fashion, the gene library may be expressed as a fusion protein on the surface of a viral particle. For instance, in the filamentous phage system, foreign peptide sequences may be expressed on the surface of infectious phage, thereby conferring two benefits. First, because these phage may be applied to affinity matrices at very high concentrations, a large number of phage may be screened at one time. Second, because each infectious phage displays the combinatorial gene product on its surface, if a particular phage is recovered from an affinity matrix in low yield, the phage may be amplified by another round of infection. The group of almost identical *E. coli* filamentous phages M13, fd, and fl are most often used in phage display libraries, as either of the phage gIII or gVIII coat proteins may be used to generate fusion proteins without disrupting the ultimate packaging of the viral particle (Ladner et al., PCT publication WO 90/02909; Garrard et al., PCT publication WO 92/09690; Marks et al., (1992) *J. Biol. Chem.* 267:16007-16010; Griffiths et al., (1993) *EMBO J.* 12:725-734; Clackson et al., (1991) *Nature* 352:624-628; and Barbas et al., (1992) *PNAS USA* 89:4457-4461). Other phage coat proteins may be used as appropriate.

The invention also provides for reduction of the polypeptides of the invention to generate mimetics, e.g. peptide or non-peptide agents, which are able to mimic binding of the authentic protein to another cellular partner. Such mutagenic techniques as described above, as well as the thioredoxin system, are also particularly useful for mapping the determinants of a protein which participates in a protein-protein interaction with another protein. To illustrate, the critical residues of a protein which are involved in molecular recognition of a substrate protein may be determined and used to generate peptidomimetics that may bind to the substrate protein. The peptidomimetic may then be used as an inhibitor of the wild-type protein by binding to the substrate and covering up the critical residues needed for interaction with the wild-type protein, thereby preventing interaction of the protein and the substrate. By employing, for example, scanning mutagenesis to map the amino acid residues of a protein which are involved in binding a substrate polypeptide,

peptidomimetic compounds may be generated which mimic those residues in binding to the substrate. For instance, non-hydrolyzable peptide analogs of such residues may be generated using benzodiazepine (e.g., see Freidinger et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted gamma lactam rings (Garvey et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al., (1986) *J. Med. Chem.* 29:295; and Ewenson et al., in *Peptides: Structure and Function* (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, IL, 1985), β-turn dipeptide cores (Nagai et al., (1985) *Tetrahedron Lett* 26:647; and Sato et al., (1986) *J Chem Soc Perkin Trans* 1:1231), and β-aminoalcohols (Gordon et al., (1985) *Biochem Biophys Res Commun* 126:419; and Dann et al., (1986) *Biochem Biophys Res Commun* 134:71).

The activity of a polypeptide of the invention may be identified and/or assayed using a variety of methods well known to the skilled artisan. For example, information about the activity of non-essential genes may be assayed by creating a null mutant strain of bacteria expressing a mutant form of, or lacking expression of, a protein of interest. The resulting phenotype of the null mutant strain may provide information about the activity of the mutated gene product. Essential genes may be studied by creating a bacterial strain with a conditional mutation in the gene of interest. The bacterial strain may be grown under permissive and non-permissive conditions and the change in phenotype under the non-permissive conditions may be used to identify and/or assay the activity of the gene product.

In an alternative embodiment, the activity of a protein may be assayed using an appropriate substrate or binding partner or other reagent suitable to test for the suspected activity. For catalytic activity, the assay is typically designed so that the enzymatic reaction produces a detectable signal. For example, mixture of a kinase with a substrate in the presence of ^{32}P will result in incorporation of the ^{32}P into the substrate. The labeled substrate may then be separated from the free ^{32}P and the presence and/or amount of radiolabeled substrate may be detected using a scintillation counter or a phosphorimager. Similar assays may be designed to identify and/or assay the activity of a wide variety of enzymatic activities. Based on the teachings herein, the skilled artisan would readily be able to develop an appropriate assay for a polypeptide of the invention.

In another embodiment, the activity of a polypeptide of the invention may be determined by assaying for the level of expression of RNA and/or protein molecules. Transcription levels may be determined, for example, using Northern blots, hybridization to an oligonucleotide array or by assaying for the level of a resulting protein product. Translation levels may be determined, for example, using Western blotting or by identifying a detectable signal produced by a protein product (e.g., fluorescence, luminescence, enzymatic activity, etc.). Depending on the particular situation, it may be desirable to detect the level of transcription and/or translation of a single gene or of multiple genes.

Alternatively, it may be desirable to measure the overall rate of DNA replication, transcription and/or translation in a cell. In general this may be accomplished by growing the cell in the presence of a detectable metabolite which is incorporated into the resultant DNA, RNA, or protein product. For example, the rate of DNA synthesis may be determined by growing cells in the presence of BrdU which is incorporated into the newly synthesized DNA. The amount of BrdU may then be determined histochemically using an anti-BrdU antibody.

In general, the biological activity of a polypeptide encoded by SEQ ID NO: 2 or SEQ ID NO: 4, and possibly other polypeptides of the invention, is triosephosphate isomerase, having the gene designation of *tpiA*. The polypeptide encoded by SEQ ID NO: 2 or SEQ ID NO: 4, and possibly other polypeptides of the invention, may be further characterized as being part of the COG category "carbohydrate transport and metabolism", with COG ID No. COG0149. The foregoing annotations were determined in accordance with the procedure described in EXAMPLE 16. This functionality asignment has been confirmed by completion of the X-ray structure of a polypeptide of the invention, as described in more detail below. In one aspect, the present invention contemplates a polypeptide having biological activity, or is a component of a protein complex having biological activity, substantially similar to or identical to triosephosphate isomerase. Alternatively, the polypeptide catalyzes, or is a component of a protein complex that catalyzes, a reaction that is substantially the same type of, or is the same as, the reaction catalyzed by triosephosphate isomerase. Other biological activities of polypeptides of the invention are described herein, or will be reasonably apparent to those skilled in the art in light of the present disclosure.

Glycolysis, in addition to its role as a important biological route for the metabolism of hexoses, provides the cell with intermediates of central metabolism for the synthesis of amino acids, vitamins, nucleotides, and cell wall constituents. Triosephosphate isomerase (TPI, EC 5.3.1.1) catalyzes interconversion of glyceraldehydes-3-phosphate and dihydroxyacetone phosphate, both formed from catabolism of fructose-1,6-diphosphate. The main metabolic role for this enzyme is to convert essentially nonmetabolizing dihydroxyacetonephosphate into glyceraldehyde-3-phosphate. By playing a critical role, such an enzyme presents a favorable target for therapeutics and diagnostics.

3. Nucleic Acids of the Invention

One aspect of the invention pertains to isolated nucleic acids of the invention. For example, the present invention contemplates an isolated nucleic acid comprising (a) the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, (b) a nucleotide sequence at least 80% identical to SEQ ID NO: 1 or SEQ ID NO: 3, (c) a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or (d) the complement of the nucleotide sequence of (a), (b) or (c). In certain embodiments, nucleic acids of the invention may be labeled, with for example, a radioactive, chemiluminescent or fluorescent label.

It may be that case that the nucleic acid sequence of SEQ ID NO: 3 differs from that of SEQ ID NO: 1 by one or more nucleic acid residues. SEQ ID NO: 3 is determined experimetally, and SEQ ID NO: 1 obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific nucleic acid sequences of SEQ ID NO: 1 and SEQ ID NO: 3, and variants thereof, as well as any differences in the applicable amino acid sequences encoded thereby.

In another aspect, the present invention contemplates an isolated nucleic acid that specifically hybridizes under stringent conditions to at least ten nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof, which nucleic acid can specifically detect or amplify SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. In yet another aspect, the present invention contemplates such an isolated nucleic acid comprising a nucleotide sequence encoding a fragment of SEQ ID NO: 2 or SEQ ID NO: 4 at least 8 residues in length. The present invention further contemplates a method of hybridizing an oligonucleotide with a nucleic acid of the invention comprising: (a) providing a single-

stranded oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; and (b) contacting the oligonucleotide with a sample comprising a nucleic acid of the acid under conditions that permit hybridization of the oligonucleotide with the nucleic acid of the invention.

Isolated nucleic acids which differ from the nucleic acids of the invention due to degeneracy in the genetic code are also within the scope of the invention. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in "silent" mutations which do not affect the amino acid sequence of the protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the polypeptides of the invention will exist. One skilled in the art will appreciate that these variations in one or more nucleotides (from less than 1% up to about 3 or 5% or possibly more of the nucleotides) of the nucleic acids encoding a particular protein of the invention may exist among a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this invention.

Bias in codon choice within genes in a single species appears related to the level of expression of the protein encoded by that gene. Accordingly, the invention encompasses nucleic acid sequences which have been optimized for improved expression in a host cell by altering the frequency of codon usage in the nucleic acid sequence to approach the frequency of preferred codon usage of the host cell. Due to codon degeneracy, it is possible to optimize the nucleotide sequence without affecting the amino acid sequence of an encoded polypeptide. Accordingly, the instant invention relates to any nucleotide sequence that encodes all or a substantial portion of the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4 or other polypeptides of the invention.

The present invention pertains to nucleic acids encoding proteins derived from *P. aeruginosa* and which have amino acid sequences evolutionarily related to a polypeptide of the invention, wherein "evolutionarily related to", refers to proteins having different amino acid sequences which have arisen naturally (e.g. by allelic variance or by differential splicing), as well as mutational variants of the proteins of the invention which are derived, for example, by combinatorial mutagenesis.

Fragments of the polynucleotides of the invention encoding a biologically active portion of the subject polypeptides are also within the scope of the invention. As used herein, a fragment of a nucleic acid of the invention encoding an active portion of a polypeptide of the invention refers to a nucleotide sequence having fewer nucleotides than the nucleotide sequence encoding the full length amino acid sequence of a polypeptide of the invention, for example, SEQ ID NO: 2 or SEQ ID NO: 4, and which encodes a polypeptide which retains at least a portion of a biological activity of the full-length protein as defined herein, or alternatively, which is functional as a modulator of the biological activity of the full-length protein. For example, such fragments include a polypeptide containing a domain of the full-length protein from which the polypeptide is derived that mediates the interaction of the protein with another molecule (e.g., polypeptide, DNA, RNA, etc.). In another embodiment, the present invention contemplates an isolated nucleic acid that encodes a polypeptide having a biological activity of a protein having the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or alternatively biological activity of triosephosphate isomerase.

Nucleic acids within the scope of the invention may also contain linker sequences, modified restriction endonuclease sites and other sequences useful for molecular cloning, expression or purification of such recombinant polypeptides.

A nucleic acid encoding a polypeptide of the invention may be obtained from mRNA or genomic DNA from any organism in accordance with protocols described herein, as well as those generally known to those skilled in the art. A cDNA encoding a polypeptide of the invention, for example, may be obtained by isolating total mRNA from an organism, e.g. a bacteria, virus, mammal, etc. Double stranded cDNAs may then be prepared from the total mRNA, and subsequently inserted into a suitable plasmid or bacteriophage vector using any one of a number of known techniques. A gene encoding a polypeptide of the invention may also be cloned using established polymerase chain reaction techniques in accordance with the nucleotide sequence information provided by the invention. In one aspect, the present invention contemplates a method for amplification of a nucleic acid of the invention, or a fragment thereof, comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length, complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides with a sample comprising a nucleic acid comprising the

nucleic acid of the invention under conditions which permit amplification of the region located between the pair of oligonucleotides, thereby amplifying the nucleic acid.

Another aspect of the invention relates to the use of nucleic acids of the invention in "antisense therapy". As used herein, antisense therapy refers to administration or *in situ* generation of oligonucleotide probes or their derivatives which specifically hybridize or otherwise bind under cellular conditions with the cellular mRNA and/or genomic DNA encoding one of the polypeptides of the invention so as to inhibit expression of that polypeptide, e.g. by inhibiting transcription and/or translation. The binding may be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, antisense therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific binding to oligonucleotide sequences.

An antisense construct of the present invention may be delivered, for example, as an expression plasmid which, when transcribed in the cell, produces RNA which is complementary to at least a unique portion of the mRNA which encodes a polypeptide of the invention. Alternatively, the antisense construct may be an oligonucleotide probe which is generated *ex vivo* and which, when introduced into the cell causes inhibition of expression by hybridizing with the mRNA and/or genomic sequences encoding a polypeptide of the invention. Such oligonucleotide probes may be modified oligonucleotides which are resistant to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patents 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy have been reviewed, for example, by van der Krol et al., (1988) *Biotechniques* 6:958-976; and Stein et al., (1988) *Cancer Res* 48:2659-2668.

In a further aspect, the invention provides double stranded small interfering RNAs (siRNAs), and methods for administering the same. siRNAs decrease or block gene expression. While not wishing to be bound by theory, it is generally thought that siRNAs inhibit gene expression by mediating sequence specific mRNA degradation. RNA interference (RNAi) is the process of sequence-specific, post-transcriptional gene silencing, particularly in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene (Elbashir et al. Nature 2001; 411(6836): 494-

8). Accordingly, it is understood that siRNAs and long dsRNAs having substantial sequence identity to all or a portion of SEQ ID NO: 1 or SEQ ID NO: 3 may be used to inhibit the expression of a nucleic acid of the invention, and particularly when the polynucleotide is expressed in a mammalian or plant cell.

The nucleic acids of the invention may be used as diagnostic reagents to detect the presence or absence of the target DNA or RNA sequences to which they specifically bind, such as for determining the level of expression of a nucleic acid of the invention. In one aspect, the present invention contemplates a method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing an oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; (b) contacting the oligonucleotide with a sample comprising at least one nucleic acid under conditions that permit hybridization of the oligonucleotide with a nucleic acid comprising a nucleotide sequence complementary thereto; and (c) detecting hybridization of the oligonucleotide to a nucleic acid in the sample, thereby detecting the presence of a nucleic acid of the invention or a portion thereof in the sample. In another aspect, the present invention contemplates a method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length, complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides with a sample comprising at least one nucleic acid under hybridization conditions; (c) amplifying the nucleotide sequence between the two oligonucleotide primers; and (d) detecting the presence of the amplified sequence, thereby detecting the presence of a nucleic acid comprising the nucleic acid of the invention or a portion thereof in the sample.

In another aspect of the invention, the subject nucleic acid is provided in an expression vector comprising a nucleotide sequence encoding a polypeptide of the invention and operably linked to at least one regulatory sequence. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. The vector's copy number, the ability to control that copy number and the expression of any other protein encoded by the vector, such as antibiotic markers, should be considered.

The subject nucleic acids may be used to cause expression and over-expression of a polypeptide of the invention in cells propagated in culture, e.g. to produce proteins or polypeptides, including fusion proteins or polypeptides.

This invention pertains to a host cell transfected with a recombinant gene in order to express a polypeptide of the invention. The host cell may be any prokaryotic or eukaryotic cell. For example, a polypeptide of the invention may be expressed in bacterial cells, such as *E. coli*, insect cells (baculovirus), yeast, or mammalian cells. In those instances when the host cell is human, it may or may not be in a live subject. Other suitable host cells are known to those skilled in the art. Additionally, the host cell may be supplemented with tRNA molecules not typically found in the host so as to optimize expression of the polypeptide. Other methods suitable for maximizing expression of the polypeptide will be known to those in the art.

The present invention further pertains to methods of producing the polypeptides of the invention. For example, a host cell transfected with an expression vector encoding a polypeptide of the invention may be cultured under appropriate conditions to allow expression of the polypeptide to occur. The polypeptide may be secreted and isolated from a mixture of cells and medium containing the polypeptide. Alternatively, the polypeptide may be retained cytoplasmically and the cells harvested, lysed and the protein isolated.

A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art. The polypeptide may be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins, including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for particular epitopes of a polypeptide of the invention.

Thus, a nucleotide sequence encoding all or a selected portion of polypeptide of the invention, may be used to produce a recombinant form of the protein via microbial or eukaryotic cellular processes. Ligating the sequence into a polynucleotide construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures. Similar procedures, or modifications thereof, may be employed to prepare recombinant polypeptides of the invention by microbial means or tissue-culture technology.

Expression vehicles for production of a recombinant protein include plasmids and other vectors. For instance, suitable vectors for the expression of a polypeptide of the invention include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for expression in prokaryotic cells, such as *E. coli.*

A number of vectors exist for the expression of recombinant proteins in yeast. For instance, YEP24, YIP5, YEP51, YEP52, pYES2, and YRP17 are cloning and expression vehicles useful in the introduction of genetic constructs into *S. cerevisiae* (see, for example, Broach et al., (1983) in *Experimental Manipulation of Gene Expression*, ed. M. Inouye Academic Press, p. 83). These vectors may replicate in *E. coli* due the presence of the pBR322 ori, and in *S. cerevisiae* due to the replication determinant of the yeast 2 micron plasmid. In addition, drug resistance markers such as ampicillin may be used.

In certain embodiments, mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. The various methods employed in the preparation of the plasmids and transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic cells, as well as general recombinant procedures, see *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant protein by the use of a baculovirus expression system. Examples of such baculovirus expression systems include pVL-derived vectors (such as pVL1392, pVL1393 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the ß-gal containing pBlueBac III).

In another variation, protein production may be achieved using *in vitro* translation systems. *In vitro* translation systems are, generally, a translation system which is a cell-free

extract containing at least the minimum elements necessary for translation of an RNA molecule into a protein. An *in vitro* translation system typically comprises at least ribosomes, tRNAs, initiator methionyl-tRNAMet, proteins or complexes involved in translation, e.g., eIF2, eIF3, the cap-binding (CB) complex, comprising the cap-binding protein (CBP) and eukaryotic initiation factor 4F (eIF4F). A variety of *in vitro* translation systems are well known in the art and include commercially available kits. Examples of *in vitro* translation systems include eukaryotic lysates, such as rabbit reticulocyte lysates, rabbit oocyte lysates, human cell lysates, insect cell lysates and wheat germ extracts. Lysates are commercially available from manufacturers such as Promega Corp., Madison, Wis.; Stratagene, La Jolla, Calif.; Amersham, Arlington Heights, Ill.; and GIBCO/BRL, Grand Island, N.Y. *In vitro* translation systems typically comprise macromolecules, such as enzymes, translation, initiation and elongation factors, chemical reagents, and ribosomes. In addition, an *in vitro* transcription system may be used. Such systems typically comprise at least an RNA polymerase holoenzyme, ribonucleotides and any necessary transcription initiation, elongation and termination factors. *In vitro* transcription and translation may be coupled in a one-pot reaction to produce proteins from one or more isolated DNAs.

When expression of a carboxy terminal fragment of a polypeptide is desired, i.e. a truncation mutant, it may be necessary to add a start codon (ATG) to the oligonucleotide fragment containing the desired sequence to be expressed. It is well known in the art that a methionine at the N-terminal position may be enzymatically cleaved by the use of the enzyme methionine aminopeptidase (MAP). MAP has been cloned from *E. coli* (Ben-Bassat et al., (1987) *J. Bacteriol.* 169:751-757) and *Salmonella typhimurium* and its *in vitro* activity has been demonstrated on recombinant proteins (Miller et al., (1987) *PNAS USA 84*:2718-1722). Therefore, removal of an N-terminal methionine, if desired, may be achieved either *in vivo* by expressing such recombinant polypeptides in a host which produces MAP (e.g., *E. coli* or CM89 or *S. cerevisiae*), or *in vitro* by use of purified MAP (e.g., procedure of Miller et al.).

Coding sequences for a polypeptide of interest may be incorporated as a part of a fusion gene including a nucleotide sequence encoding a different polypeptide. The present invention contemplates an isolated nucleic acid comprising a nucleic acid of the invention and at least one heterologous sequence encoding a heterologous peptide linked in frame to the nucleotide sequence of the nucleic acid of the invention so as to encode a fusion protein comprising the heterologous polypeptide. The heterologous polypeptide may be fused to

(a) the C-terminus of the polypeptide encoded by the nucleic acid of the invention, (b) the N-terminus of the polypeptide, or (c) the C-terminus and the N-terminus of the polypeptide. In certain instances, the heterologous sequence encodes a polypeptide permitting the detection, isolation, solubilization and/or stabilization of the polypeptide to which it is fused. In still other embodiments, the heterologous sequence encodes a polypeptide selected from the group consisting of a polyHis tag, myc, HA, GST, protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose-binding protein, poly arginine, poly His-Asp, FLAG, a portion of an immunoglobulin protein, and a transcytosis peptide.

Fusion expression systems can be useful when it is desirable to produce an immunogenic fragment of a polypeptide of the invention. For example, the VP6 capsid protein of rotavirus may be used as an immunologic carrier protein for portions of polypeptide, either in the monomeric form or in the form of a viral particle. The nucleic acid sequences corresponding to the portion of a polypeptide of the invention to which antibodies are to be raised may be incorporated into a fusion gene construct which includes coding sequences for a late vaccinia virus structural protein to produce a set of recombinant viruses expressing fusion proteins comprising a portion of the protein as part of the virion. The Hepatitis B surface antigen may also be utilized in this role as well. Similarly, chimeric constructs coding for fusion proteins containing a portion of a polypeptide of the invention and the poliovirus capsid protein may be created to enhance immunogenicity (see, for example, EP Publication NO: 0259149; and Evans et al., (1989) *Nature* 339:385; Huang et al., (1988) *J. Virol.* 62:3855; and Schlienger et al., (1992) *J. Virol.* 66:2).

Fusion proteins may facilitate the expression and/or purification of proteins. For example, a polypeptide of the invention may be generated as a glutathione-S-transferase (GST) fusion protein. Such GST fusion proteins may be used to simplify purification of a polypeptide of the invention, such as through the use of glutathione-derivatized matrices (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., (N.Y.: John Wiley & Sons, 1991)). In another embodiment, a fusion gene coding for a purification leader sequence, such as a poly-(His)/enterokinase cleavage site sequence at the N-terminus of the desired portion of the recombinant protein, may allow purification of the expressed fusion protein by affinity chromatography using a Ni^{2+} metal resin. The purification leader sequence may then be subsequently removed by treatment with enterokinase to provide the purified protein (e.g., see Hochuli et al., (1987) *J. Chromatography* 411: 177; and Janknecht et al., *PNAS USA* 88:8972).

Techniques for making fusion genes are well known. Essentially, the joining of various DNA fragments coding for different polypeptide sequences is performed in accordance with conventional techniques, employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene may be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments may be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which may subsequently be annealed to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., John Wiley & Sons: 1992).

The present invention further contemplates a transgenic non-human animal having cells which harbor a transgene comprising a nucleic acid of the invention.

In other embodiments, the invention provides for nucleic acids of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The nucleic acids of the invention may be immobilized onto a chip as part of an array. The array may comprise one or more polynucleotides of the invention as described herein. In one embodiment, the chip comprises one or more polynucleotides of the invention as part of an array of *P. aeruginosa* polynucleotide sequences.

In still other embodiments, the invention comprises the sequence of a nucleic acid of the invention in computer readable format. The invention also encompasses a database comprising the sequence of a nucleic acid of the invention.

4. Homology Searching of Nucleotide and Polypeptide Sequences

The nucleotide or amino acid sequences of the invention may be used as query sequences against databases such as GenBank, SwissProt, PDB, BLOCKS, and Pima II. These databases contain previously identified and annotated sequences that may be searched for regions of homology (similarity) using BLAST, which stands for Basic Local Alignment Search Tool (Altschul S F (1993) J Mol Evol 36:290-300; Altschul, S F et al (1990) J Mol Biol 215:403-10).

BLAST produces alignments of both nucleotide and amino acid sequences to determine sequence similarity. Because of the local nature of the alignments, BLAST is especially useful in determining exact matches or in identifying homologs which may be of prokaryotic (bacterial) or eukaryotic (animal, fungal or plant) origin. Other algorithms such as the one described in Smith, R. F. and T. F. Smith (1992; Protein Engineering 5:35-51) may be used when dealing with primary sequence patterns and secondary structure gap penalties. In the usual course using BLAST, sequences have lengths of at least 49 nucleotides and no more than 12% uncalled bases (where N is recorded rather than A, C, G, or T).

The BLAST approach, as detailed in Karlin and Altschul (1993; Proc Nat Acad Sci 90:5873-7) searches matches between a query sequence and a database sequence, to evaluate the statistical significance of any matches found, and to report only those matches which satisfy the user-selected threshold of significance. The threshold is typically set at about 10-25 for nucleotides and about 3-15 for peptides.

5. *Analysis of Protein Properties*

(a) *Analysis of Proteins by Mass Spectrometry*

Typically, protein characterization by mass spectroscopy first requires protein isolation followed by either chemical or enzymatic digestion of the protein into smaller peptide fragments, whereupon the peptide fragments may be analyzed by mass spectrometry to obtain a peptide map. Mass spectrometry may also be used to identify post-translational modifications (e.g., phosphorylation, etc.) of a polypeptide.

Various mass spectrometers may be used within the present invention. Representative examples include: triple quadrupole mass spectrometers, magnetic sector instruments (magnetic tandem mass spectrometer, JEOL, Peabody, Mass), ionspray mass spectrometers (Bruins et al., Anal Chem. 59:2642-2647, 1987), electrospray mass spectrometers (including tandem, nano- and nano-electrospray tandem) (Fenn et al., Science 246:64-71, 1989), laser desorption time-of-flight mass spectrometers (Karas and Hillenkamp, Anal. Chem. 60:2299-2301, 1988), and a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (Extrel Corp., Pittsburgh, Mass.).

MALDI ionization is a technique in which samples of interest, in this case peptides and proteins, are co-crystallized with an acidified matrix. The matrix is typically a small molecule that absorbs at a specific wavelength, generally in the ultraviolet (UV) range, and dissipates the absorbed energy thermally. Typically a pulsed laser beam is used to transfer energy rapidly (i.e., a few ns) to the matrix. This transfer of energy causes the matrix to rapidly dissociate from the MALDI plate surface and results in a plume of matrix and the co-crystallized analytes being transferred into the gas phase. MALDI is considered a "soft-ionization" method that typically results in singly-charged species in the gas phase, most often resulting from a protonation reaction with the matrix. MALDI may be coupled in-line with time of flight (TOF) mass spectrometers. TOF detectors are based on the principle that an analyte moves with a velocity proportional to its mass. Analytes of higher mass move slower than analytes of lower mass and thus reach the detector later than lighter analytes. The present invention contemplates a composition comprising a polypeptide of the invention and a matrix suitable for mass spectrometry. In certain instances, the matrix is a nicotinic acid derivative or a cinnamic acid derivative.

MALDI-TOF MS is easily performed with modern mass spectrometers. Typically the samples of interest, in this case peptides or proteins, are mixed with a matrix and spotted onto a polished stainless steel plate (MALDI plate). Commercially available MALDI plates can presently hold up to 1536 samples per plate. Once spotted with sample, the MALDI sample plate is then introduced into the vacuum chamber of a MALDI mass spectrometer. The pulsed laser is then activated and the mass to charge ratios of the analytes are measured utilizing a time of flight detector. A mass spectrum representing the mass to charge ratios of the peptides/proteins is generated.

As mentioned above, MALDI can be utilized to measure the mass to charge ratios of both proteins and peptides. In the case of proteins, a mixture of intact protein and matrix are co-crystallized on a MALDI target (Karas, M. and Hillenkamp, F. Anal. Chem. 1988, 60 (20) 2299-2301). The spectrum resulting from this analysis is employed to determine the molecular weight of a whole protein. This molecular weight can then be compared to the theoretical weight of the protein and utilized in characterizing the analyte of interest, such as whether or not the protein has undergone post-translational modifications (e.g., example phosphorylation).

In certain embodiments, MALDI mass spectrometry is used for determination of peptide maps of digested proteins. The peptide masses are measured accurately using a

MALDI-TOF or a MALDI-Q-Star mass spectrometer, with detection precision down to the low ppm (parts per million) level. The ensemble of the peptide masses observed in a protein digest, such as a tryptic digest, may be used to search protein/DNA databases in a method called peptide mass fingerprinting. In this approach, protein entries in a database are ranked according to the number of experimental peptide masses that match the predicted trypsin digestion pattern. Commercially available software utilizes a search algorithm that provides a scoring scheme based on the size of the databases, the number of matching peptides, and the different peptides. Depending on the number of peptides observed, the accuracy of the measurement, and the size of the genome of the particular species, unambiguous protein identification may be obtained.

Statistical analysis may be performed upon each protein match to determine the validity of the match. Typical constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, cysteines may be alkylated and searched as carboxyamidomethyl modifications, 0 or 1 missed enzyme cleavages, and no methionine oxidations allowed. Identified proteins may be stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences. Often even a partial peptide map is specific enough for identification of the protein. If no protein match is found, a more error-tolerant search can be used, for example using fewer peptides or allowing a larger margin error with respect to mass accuracy.

Other mass spectroscopy methods such as tandem mass spectrometry or post source decay may be used to obtain sequence information about proteins that cannot be identified by peptide mass mapping, or to confirm the identity of proteins that are tentatively identified by an error-tolerant peptide mass search described above. (Griffin et al, Rapid Commun. Mass. Spectrom. 1995, 9, 1546-51).

(b) Analysis of Proteins by Nuclear Magnetic Resonance (NMR)

NMR may be used to characterize the structure of a polypeptide in accordance with the methods of the invention. In particular, NMR can be used, for example, to determine the three dimensional structure, the conformational state, the aggregation level, the state of protein folding/unfolding or the dynamic properties of a polypeptide. For example, the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention; and (b) subjecting the

polypeptide to NMR spectroscopic analysis, thereby determining information about its three dimensional structure.

Interaction between a polypeptide and another molecule can also be monitored using NMR. Thus, the invention encompasses methods for detecting, designing and characterizing interactions between a polypeptide and another molecule, including polypeptides, nucleic acids and small molecules, utilizing NMR techniques. For example, the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, or a fragment thereof, while the polypeptide is complexed with another molecule, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention, or a fragment thereof; (b) forming a complex between the polypeptide and the other molecule; and (c) subjecting the complex to NMR spectroscopic analysis, thereby determining information about the three dimensional structure of the polypeptide. In another aspect, the present invention contemplates a method for identifying compounds that bind to a polypeptide of the invention, or a fragment thereof, the method comprising: (a) generating a first NMR spectrum of an isotopically labeled polypeptide of the invention, or a fragment thereof; (b) exposing the polypeptide to one or more chemical compounds; (c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more chemical compounds; and (d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more compounds that have bound to the polypeptide.

Briefly, the NMR technique involves placing the material to be examined (usually in a suitable solvent) in a powerful magnetic field and irradiating it with radio frequency (rf) electromagnetic radiation. The nuclei of the various atoms will align themselves with the magnetic field until energized by the rf radiation. They then absorb this resonant energy and re-radiate it at a frequency dependent on i) the type of nucleus and ii) its atomic environment. Moreover, resonant energy may be passed from one nucleus to another, either through bonds or through three-dimensional space, thus giving information about the environment of a particular nucleus and nuclei in its vicinity.

However, it is important to recognize that not all nuclei are NMR active. Indeed, not all isotopes of the same element are active. For example, whereas "ordinary" hydrogen, ^{1}H, is NMR active, heavy hydrogen (deuterium), ^{2}H, is not active in the same way. Thus, any material that normally contains ^{1}H hydrogen may be rendered "invisible" in the

hydrogen NMR spectrum by replacing all or almost all the ^1H hydrogens with ^2H. It is for this reason that NMR spectroscopic analyses of water-soluble materials frequently are performed in ^2H_2O (or deuterium) to eliminate the water signal.

Conversely, "ordinary" carbon, ^{12}C, is NMR inactive whereas the stable isotope, ^{13}C, present to about 1% of total carbon in nature, is active. Similarly, while "ordinary" nitrogen, ^{14}N, is NMR active, it has undesirable properties for NMR and resonates at a different frequency from the stable isotope ^{15}N, present to about 0.4% of total nitrogen in nature.

By labeling proteins with ^{15}N and $^{15}N/^{13}C$, it is possible to conduct analytical NMR of macromolecules with weights of 15 kD and 40 kD, respectively. More recently, partial deuteration of the protein in addition to ^{13}C- and ^{15}N-labeling has increased the possible weight of proteins and protein complexes for NMR analysis still further, to approximately 60-70 kD. See Shan et al., J. Am. Chem.Soc., 118:6570-6579 (1996); L.E. Kay, Methods Enzymol., 339:174-203 (2001); and K.H. Gardner & L.E. Kay, Annu Rev Biophys Biomol Struct., 27:357-406 (1998); and references cited therein.

Isotopic substitution may be accomplished by growing a bacterium or yeast or other type of cultured cells, transformed by genetic engineering to produce the protein of choice, in a growth medium containing ^{13}C-, ^{15}N- and/or ^2H-labeled substrates. In certain instances, bacterial growth media consists of ^{13}C-labeled glucose and/or ^{15}N-labeled ammonium salts dissolved in D_2O where necessary. Kay, L. et al., Science, 249:411 (1990) and references therein and Bax, A., J. Am. Chem. Soc., 115, 4369 (1993). More recently, isotopically labeled media especially adapted for the labeling of bacterially produced macromolecules have been described. See U.S. Pat. No. 5,324,658.

The goal of these methods has been to achieve universal and/or random isotopic enrichment of all of the amino acids of the protein. By contrast, other methods allow only certain residues to be relatively enriched in ^1H, ^2H, ^{13}C and ^{15}N. For example, Kay et al., J. Mol. Biol., 263, 627-636 (1996) and Kay et al., J. Am. Chem. Soc., 119, 7599-7600 (1997) have described methods whereby isoleucine, alanine, valine and leucine residues in a protein may be labeled with ^2H, ^{13}C and ^{15}N and may be specifically labeled with ^1H at the terminal methyl position. In this way, study of the proton-proton interactions between some amino acids may be facilitated. Similarly, a cell-free system has been described by Yokoyama et al., J. Biomol. NMR, 6(2), 129-134 (1995)., wherein a transcription-

translation system derived from E. coli was used to express human Ha-Ras protein incorporating ^{15}N into serine and/or aspartic acid.

Techniques for producing isotopically labeled proteins and macromolecules, such as glycoproteins, in mammalian or insect cells have been described. See U.S. Pat. Nos. 5,393,669 and 5,627,044; Weller, C. T., Biochem., 35, 8815-23 (1996) and Lustbader, J. W., J.Biomol. NMR, 7, 295-304 (1996). Other methods for producing polypeptides and other molecules with labels appropriate for NMR are known in the art.

The present invention contemplates using a variety of solvents which are appropriate for NMR. For ^{1}H NMR, a deuterium lock solvent may be used. Exemplary deuterium lock solvents include acetone (CD_3COCD_3), chloroform ($CDCl_3$), dichloro methane (CD_2Cl_2), methylnitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether ($(CD_3CD_2)_2O$), dimethylether ($(CD_3)_2O$), N,N-dimethylformamide ($(CD_3)_2NCDO$), dimethyl sulfoxide (CD_3SOCD_3), ethanol (CD_3CD_2OD), methanol (CD_3OD), tetrahydrofuran (C_4D_8O), toluene ($C_6D_5CD_3$), pyridine (C_5D_5N) and cyclohexane (C_6H_{12}). For example, the present invention contemplates a composition comprising a polypeptide of the invention and a deuterium lock solvent.

The 2-dimensional ^{1}H-^{15}N HSQC (Heteronuclear Single Quantum Correlation) spectrum provides a diagnostic fingerprint of conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide (Yee et al, PNAS 99, 1825-30 (2002)). Polypeptides in aqueous solution usually populate an ensemble of 3-dimensional structures which can be determined by NMR. When the polypeptide is a stable globular protein or domain of a protein, then the ensemble of solution structures is one of very closely related conformations. In this case, one peak is expected for each non-proline residue with a dispersion of resonance frequencies with roughly equal intensity. Additional pairs of peaks from side-chain NH2 groups are also often observed, and correspond to the approximate number of Gln and Asn residues in the protein. This type of HSQC spectra usually indicates that the protein is amenable to structure determination by NMR methods.

If the HSQC spectrum shows well-dispersed peaks but there are either too few or too many in number, and/or the peak intensities differ throughout the spectrum, then the protein likely does not exist in a single globular conformation. Such spectral features are indicative of conformational heterogeneity with slow or nonexistent inter-conversion between states (too many peaks) or the presence of dynamic processes on an intermediate

timescale that can broaden and obscure the NMR signals. Proteins with this type of spectrum can sometimes be stabilized into a single conformation by changing either the protein construct, the solution conditions, temperature or by binding of another molecule.

The ^{1}H-^{15}N HSQC can also indicate whether a protein has formed large nonspecific aggregates or has dynamic properties. Alternatively, proteins that are largely unfolded, e.g., having very little regular secondary structure, result in ^{1}H-^{15}N HSQC spectra in which the peaks are all very narrow and intense, but have very little spectral dispersion in the ^{15}N-dimension. This reflects the fact that many or most of the amide groups of amino acids in unfolded polypeptides are solvent exposed and experience similar chemical environments resulting in similar ^{1}H chemical shifts.

The use of the ^{1}H-^{15}N HSQC, can thus allow the rapid characterization of the conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide. Additionally, other 2D spectra such as ^{1}H-^{13}C HSQC, or HNCO spectra can also be used in a similar manner. Further use of the ^{1}H-^{15}N HSQC combined with relaxation measurements can reveal the molecular rotational correlation time and dynamic properties of polypeptides. The rotational correlation time is proportional to size of the protein and therefore can reveal if it forms specific homo-oligomers such as homodimers, homotetramers, etc.

The structure of stable globular proteins can be determined through a series of well-described procedures. For a general review of structure determination of globular proteins in solution by NMR spectroscopy, see Wüthrich, Science 243: 45-50 (1989). See also, Billeter et al., J. Mol. Biol. 155: 321-346 (1982). Current methods for structure determination usually require the complete or nearly complete sequence-specific assignment of ^{1}H-resonance frequencies of the protein and subsequent identification of approximate inter-hydrogen distances (from nuclear Overhauser effect (NOE) spectra) for use in restrained molecular dynamics calculations of the protein conformation. One approach for the analysis of NMR resonance assignments was first outlined by Wüthrich, Wagner and co-workers (Wüthrich, "NMR or proteins and nucleic acids" Wiley, New York, New York (1986); Wüthrich, Science 243: 45-50 (1989); Billeter et al., J. Mol. Biol. 155: 321-346 (1982)). Newer methods for determining the structures of globular proteins include the use of residual dipolar coupling restraints (Tian et al., J Am Chem Soc. 2001 Nov 28;123(47):11791-6; Bax et al, Methods Enzymol. 2001;339:127-74) and empirically derived conformational restraints (Zweckstetter & Bax, J Am Chem Soc. 2001 Sep

26;123(38):9490-1). It has also been shown that it may be possible to determine structures of globular proteins using only un-assigned NOE measurements. NMR may also be used to determine ensembles of many inter-converting, unfolded conformations (Choy and Forman-Kay, J Mol Biol. 2001 May 18;308(5):1011-32).

NMR analysis of a polypeptide in the presence and absence of a test compound (e.g., a polypeptide, nucleic acid or small molecule) may be used to characterize interactions between a polypeptide and another molecule. Because the ^{1}H-^{15}N HSQC spectrum and other simple 2D NMR experiments can be obtained very quickly (on the order of minutes depending on protein concentration and NMR instrumentation), they are very useful for rapidly testing whether a polypeptide is able to bind to another molecule. Changes in the resonance frequency (in one or both dimensions) of one or more peaks in the HSQC spectrum indicate an interaction with another molecule. Often only a subset of the peaks will have changes in resonance frequency upon binding to anther molecule, allowing one to map onto the structure those residues directly involved in the interaction or involved in conformational changes as a result of the interaction. If the interacting molecule is relatively large (protein or nucleic acid) the peak widths will also broaden due to the increased rotational correlation time of the complex. In some cases the peaks involved in the interaction may actually disappear from the NMR spectrum if the interacting molecule is in intermediate exchange on the NMR timescale (i.e., exchanging on and off the polypeptide at a frequency that is similar to the resonance frequency of the monitored nuclei).

To facilitate the acquisition of NMR data on a large number of compounds (e.g., a library of synthetic or naturally-occurring small organic compounds), a sample changer may be employed. Using the sample changer, a larger number of samples, numbering 60 or more, may be run unattended. To facilitate processing of the NMR data, computer programs are used to transfer and automatically process the multiple one-dimensional NMR data.

In one embodiment, the invention provides a screening method for identifying small molecules capable of interacting with a polypeptide of the invention. In one example, the screening process begins with the generation or acquisition of either a T_2-filtered or a diffusion-filtered one-dimensional proton spectrum of the compound or mixture of compounds. Means for generating T_2-filtered or diffusion-filtered one-dimensional proton spectra are well known in the art (see, e.g., S. Meiboom and D. Gill, Rev. Sci. Instrum.

29:688(1958), S. J. Gibbs and C. S. Johnson, Jr. J. Main. Reson. 93:395-402 (1991) and A. S. Altieri, et al. J. Am. Chem. Soc. 117: 7566-7567 (1995)).

Following acquisition of the first spectrum for the molecules, the ^{15}N- or ^{13}C-labeled polypeptide is exposed to one or more molecules. Where more than one test compound is to be tested simultaneously, it is preferred to use a library of compounds such as a plurality of small molecules. Such molecules are typically dissolved in perdeuterated dimethylsulfoxide. The compounds in the library may be purchased from vendors or created according to desired needs.

Individual compounds may be selected inter alia on the basis of size and molecular diversity for maximizing the possibility of discovering compounds that interact with widely diverse binding sites of a polypeptide of the invention.

The NMR screening process of the present invention utilizes a range of test compound concentrations, e.g., from about 0.05 to about 1.0 mM. At those exemplary concentrations, compounds which are acidic or basic may significantly change the pH of buffered protein solutions. Chemical shifts are sensitive to pH changes as well as direct binding interactions, and false-positive chemical shift changes, which are not the result of test compound binding but of changes in pH, may therefore be observed. It may therefore be necessary to ensure that the pH of the buffered solution does not change upon addition of the test compound.

Following exposure of the test compounds to a polypeptide (e.g., the target molecule for the experiment) a second one-dimensional T_2- or diffusion-filtered spectrum is generated. For the T_2-filtered approach, that second spectrum is generated in the same manner as set forth above. The first and second spectra are then compared to determine whether there are any differences between the two spectra. Differences in the one-dimensional T_2-filtered spectra indicate that the compound is binding to, or otherwise interacting with, the target molecule. Those differences are determined using standard procedures well known in the art. For the diffusion-filtered method, the second spectrum is generated by looking at the spectral differences between low and high gradient strengths--thus selecting for those compounds whose diffusion rates are comparable to that observed in the absence of target molecule.

To discover additional molecules that bind to the protein, molecules are selected for testing based on the structure/activity relationships from the initial screen and/or structural

information on the initial leads when bound to the protein. By way of example, the initial screening may result in the identification of compounds, all of which contain an aromatic ring. The second round of screening would then use other aromatic molecules as the test compounds.

In another embodiment, the methods of the invention utilize a process for detecting the binding of one ligand to a polypeptide in the presence of a second ligand. In accordance with this embodiment, a polypeptide is bound to the second ligand before exposing the polypeptide to the test compounds.

For more information on NMR methods encompassed by the present invention, see also: U.S. Patent Nos. 5,668,734; 6,194,179; 6,162,627; 6,043,024; 5,817,474; 5,891,642; 5,989,827; 5,891,643; 6,077,682; WO 00/05414; WO 99/22019; Cavanagh, et al., Protein NMR Spectroscopy, Principles and Practice, 1996, Academic Press; Clore, et al., NMR of Proteins. In Topics in Molecular and Structural Biology, 1993, S. Neidle, Fuller, W., and Cohen, J.S., eds., Macmillan Press, Ltd., London; and Christendat et al., Nature Structural Biology 7: 903-909 (2000).

(c) Analysis of Proteins by X-ray Crystallography

(i) X-ray Structure Determination

Exemplary methods for obtaining the three dimensional structure of the crystalline form of a molecule or complex are described herein and, in view of this specification, variations on these methods will be apparent to those skilled in the art (see Ducruix and Geige 1992, IRL Press, Oxford, England).

A variety of methods involving x-ray crystallography are contemplated by the present invention. For example, the present invention contemplates producing a crystallized polypeptide of the invention, or a fragment thereof, by: (a) introducing into a host cell an expression vector comprising a nucleic acid encoding for a polypeptide of the invention, or a fragment thereof; (b) culturing the host cell in a cell culture medium to express the polypeptide or fragment; (c) isolating the polypeptide or fragment from the cell culture; and (d) crystallizing the polypeptide or fragment thereof. Alternatively, the present invention contemplates determining the three dimensional structure of a crystallized polypeptide of of the invention, or a fragment thereof, by: (a) crystallizing a polypeptide of the invention, or a fragment thereof, such that the crystals will diffract x-rays to a resolution

of 3.5 Å or better; and (b) analyzing the polypeptide or fragment by x-ray diffraction to determine the three-dimensional structure of the crystallized polypeptide.

X-ray crystallography techniques generally require that the protein molecules be available in the form of a crystal. Crystals may be grown from a solution containing a purified polypeptide of the invention, or a fragment thereof (e.g., a stable domain), by a variety of conventional processes. These processes include, for example, batch, liquid, bridge, dialysis, vapour diffusion (e.g., hanging drop or sitting drop methods). (See for example, McPherson, 1982 John Wiley, New York; McPherson, 1990, Eur. J. Biochem. 189: 1-23; Webber. 1991, Adv. Protein Chem. 41:1-36).

In certain embodiments, native crystals of the invention may be grown by adding precipitants to the concentrated solution of the polypeptide. The precipitants are added at a concentration just below that necessary to precipitate the protein. Water may be removed by controlled evaporation to produce precipitating conditions, which are maintained until crystal growth ceases.

The formation of crystals is dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions or ligands to the protein. In addition, the sequence of the polypeptide being crystallized will have a significant affect on the success of obtaining crystals. Many routine crystallization experiments may be needed to screen all these parameters for the few combinations that might give crystal suitable for x-ray diffraction analysis (See, for example, Jancarik, J & Kim, S.H., J. Appl. Cryst. 1991 24: 409-411).

Crystallization robots may automate and speed up the work of reproducibly setting up large number of crystallization experiments. Once some suitable set of conditions for growing the crystal are found, variations of the condition may be systematically screened in order to find the set of conditions which allows the growth of sufficiently large, single, well ordered crystals. In certain instances, a polypeptide of the invention is co-crystallized with a compound that stabilizes the polypeptide.

A number of methods are available to produce suitable radiation for x-ray diffraction. For example, x-ray beams may be produced by synchrotron rings where electrons (or positrons) are accelerated through an electromagnetic field while traveling at close to the speed of light. Because the admitted wavelength may also be controlled, synchrotrons may be used as a tunable x-ray source (Hendrickson WA., Trends Biochem

Sci 2000 Dec; 25(12):637-43). For less conventional Laue diffraction studies, polychromatic x-rays covering a broad wavelength window are used to observe many diffraction intensities simultaneously (Stoddard, B. L., Curr. Opin. Struct Biol 1998 Oct; 8(5):612-8). Neutrons may also be used for solving protein crystal structures (Gutberlet T, Heinemann U & Steiner M., Acta Crystallogr D 2001;57: 349-54).

Before data collection commences, a protein crystal may be frozen to protect it from radiation damage. A number of different cryo-protectants may be used to assist in freezing the crystal, such as methyl pentanediol (MPD), isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil, or a low-molecular-weight polyethylene glycol (PEG). The present invention contemplates a composition comprising a polypeptide of the invention and a cryo-protectant. As an alternative to freezing the crystal, the crystal may also be used for diffraction experiments performed at temperatures above the freezing point of the solution. In these instances, the crystal may be protected from drying out by placing it in a narrow capillary of a suitable material (generally glass or quartz) with some of the crystal growth solution included in order to maintain vapour pressure.

X-ray diffraction results may be recorded by a number of ways know to one of skill in the art. Examples of area electronic detectors include charge coupled device detectors, multi-wire area detectors and phosphoimager detectors (Amemiya, Y, 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 233-243; Westbrook, E. M., Naday, I. 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 244-268; 1997. Kahn, R. & Fourme, R. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 268-286).

A suitable system for laboratory data collection might include a Bruker AXS Proteum R system, equipped with a copper rotating anode source, Confocal Max-Flux™ optics and a SMART 6000 charge coupled device detector. Collection of x-ray diffraction patterns are well documented by those skilled in the art (See, for example, Ducruix and Geige, 1992, IRL Press, Oxford, England).

The theory behind diffraction by a crystal upon exposure to x-rays is well known. Because phase information is not directly measured in the diffraction experiment, and is needed to reconstruct the electron density map, methods that can recover this missing information are required. One method of solving structures *ab initio* are the real / reciprocal space cycling techniques. Suitable real / reciprocal space cycling search

programs include shake-and-bake (Weeks CM, DeTitta GT, Hauptman HA, Thuman P, Miller R Acta Crystallogr A 1994; V50: 210-20).

Other methods for deriving phases may also be needed. These techniques generally rely on the idea that if two or more measurements of the same reflection are made where strong, measurable, differences are attributable to the characteristics of a small subset of the atoms alone, then the contributions of other atoms can be, to a first approximation, ignored, and positions of these atoms may be determined from the difference in scattering by one of the above techniques. Knowing the position and scattering characteristics of those atoms, one may calculate what phase the overall scattering must have had to produce the observed differences.

One version of this technique is isomorphous replacement technique, which requires the introduction of new, well ordered, x-ray scatterers into the crystal. These additions are usually heavy metal atoms, (so that they make a significant difference in the diffraction pattern); and if the additions do not change the structure of the molecule or of the crystal cell, the resulting crystals should be isomorphous. Isomorphous replacement experiments are usually performed by diffusing different heavy-metal metals into the channels of a pre-existing protein crystal. Growing the crystal from protein that has been soaked in the heavy atom is also possible (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156). Alternatively, the heavy atom may also be reactive and attached covalently to exposed amino acid side chains (such as the sulfur atom of cysteine) or it may be associated through non-covalent interactions. It is sometimes possible to replace endogenous light metals in metallo-proteins with heavier ones, e.g., zinc by mercury, or calcium by samarium (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156). Exemplary sources for such heavy compounds include, without limitation, sodium bromide, sodium selenate, trimethyl lead acetate, mercuric chloride, methyl mercury acetate, platinum tetracyanide, platinum tetrachloride, nickel chloride, and europium chloride.

A second technique for generating differences in scattering involves the phenomenon of anomalous scattering. X-rays that cause the displacement of an electron in an inner shell to a higher shell are subsequently rescattered, but there is a time lag that shows up as a phase delay. This phase delay is observed as a (generally quite small) difference in intensity between reflections known as Friedel mates that would be identical if no anomalous scattering were present. A second effect related to this phenomenon is that

differences in the intensity of scattering of a given atom will vary in a wavelength dependent manner, given rise to what are known as dispersive differences. In principle anomalous scattering occurs with all atoms, but the effect is strongest in heavy atoms, and may be maximized by using x-rays at a wavelength where the energy is equal to the difference in energy between shells. The technique therefore requires the incorporation of some heavy atom much as is needed for isomorphous replacement, although for anomalous scattering a wider variety of atoms are suitable, including lighter metal atoms (copper, zinc, iron) in metallo-proteins. One method for preparing a protein for anomalous scattering involves replacing the methionine residues in whole or in part with selenium containing seleno-methionine. Soaks with halide salts such as bromides and other non-reactive ions may also be effective (Dauter Z, Li M, Wlodawer A., Acta Crystallogr D 2001; 57: 239-49).

In another process, known as multiple anomalous scattering or MAD, two to four suitable wavelengths of data are collected. (Hendrickson, W.A. and Ogata, C.M. 1997 Methods in Enzymology 276, 494 – 523). Phasing by various combinations of single and multiple isomorphous and anomalous scattering are possible too. For example, SIRAS (single isomorphous replacement with anomalous scattering) utilizes both the isomorphous and anomalous differences for one derivative to derive phases. More traditionally, several different heavy atoms are soaked into different crystals to get sufficient phase information from isomorphous differences while ignoring anomalous scattering, in the technique known as multiple isomorphous replacement (MIR) (Petsko, G.A., 1985. Methods in Enzymology, Vol. 114. Academic Press, Orlando, pp. 147-156).

Additional restraints on the phases may be derived from density modification techniques. These techniques use either generally known features of electron density distribution or known facts about that particular crystal to improve the phases. For example, because protein regions of the crystal scatter more strongly than solvent regions, solvent flattening/flipping may be used to adjust phases to make solvent density a uniform flat value (Zhang, K. Y. J., Cowtan, K. and Main, P. Methods in Enzymology 277, 1997 Academic Press, Orlando pp 53-64). If more than one molecule of the protein is present in the asymmetric unit, the fact that the different molecules should be virtually identical may be exploited to further reduce phase error using non-crystallographic symmetry averaging (Villieux, F. M. D. and Read, R. J. Methods in Enzymology 277, 1997 Academic Press, Orlando pp18-52). Suitable programs for performing these processes include DM and other

programs of the CCP4 suite (Collaborative Computational Project, Number 4. 1994. Acta Cryst. D50, 760-763) and CNX.

The unit cell dimensions, symmetry, vector amplitude and derived phase information can be used in a Fourier transform function to calculate the electron density in the unit cell, i.e., to generate an experimental electron density map. This may be accomplished using programs of the CNX or CCP4 packages. The resolution is measured in Ångstrom (Å) units, and is closely related to how far apart two objects need to be before they can be reliably distinguished. The smaller this number is, the higher the resolution and therefore the greater the amount of detail that can be seen. Preferably, crystals of the invention diffract x-rays to a resolution of better than about 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5 Å or better.

As used herein, the term "modeling" includes the quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models. The term "modeling" includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models.

Model building may be accomplished by either the crystallographer using a computer graphics program such as TURBO or O (Jones, TA. et al., Acta Crystallogr. A47, 100-119, 1991) or, under suitable circumstances, by using a fully automated model building program, such as wARP (Anastassis Perrakis, Richard Morris & Victor S. Lamzin; Nature Structural Biology, May 1999 Volume 6 Number 5 pp 458 – 463) or MAID (Levitt, D. G., Acta Crystallogr. D 2001 V57: 1013-9). This structure may be used to calculate model-derived diffraction amplitudes and phases. The model-derived and experimental diffraction amplitudes may be compared and the agreement between them can be described by a parameter referred to as R-factor. A high degree of correlation in the amplitudes corresponds to a low R-factor value, with 0.0 representing exact agreement and 0.59 representing a completely random structure. Because the R-factor may be lowered by introducing more free parameters into the model, an unbiased, cross-correlated version of the R-factor known as the R-free gives a more objective measure of model quality. For the calculation of this parameter a subset of reflections (generally around 10%) are set aside at the beginning of the refinement and not used as part of the refinement target. These

reflections are then compared to those predicted by the model (Kleywegt GJ, Brunger AT, Structure 1996 Aug 15;4(8):897-904).

The model may be improved using computer programs that maximize the probability that the observed data was produced from the predicted model, while simultaneously optimizing the model geometry. For example, the CNX program may be used for model refinement, as can the XPLOR program (1992, Nature 355:472-475, G.N. Murshudov, A.A.Vagin and E.J.Dodson, (1997) Acta Cryst. D 53, 240-255). In order to maximize the convergence radius of refinement, simulated annealing refinement using torsion angle dynamics may be employed in order to reduce the degrees of freedom of motion of the model (Adams PD, Pannu NS, Read RJ, Brunger AT., Proc Natl Acad Sci U S A 1997 May 13;94(10):5018-23). Where experimental phase information is available (e.g. where MAD data was collected) Hendrickson-Lattman phase probability targets may be employed. Isotropic or anisotropic domain, group or individual temperature factor refinement, may be used to model variance of the atomic position from its mean. Well defined peaks of electron density not attributable to protein atoms are generally modeled as water molecules. Water molecules may be found by manual inspection of electron density maps, or with automatic water picking routines. Additional small molecules, including ions, cofactors, buffer molecules or substrates may be included in the model if sufficiently unambiguous electron density is observed in a map.

In general, the R-free is rarely as low as 0.15 and may be as high as 0.35 or greater for a reasonably well-determined protein structure. The residual difference is a consequence of approximations in the model (inadequate modeling of residual structure in the solvent, modeling atoms as isotropic Gaussian spheres, assuming all molecules are identical rather than having a set of discrete conformers, etc.) and errors in the data (Lattman EE., Proteins 1996; 25: i-ii). In refined structures at high resolution, there are usually no major errors in the orientation of individual residues, and the estimated errors in atomic positions are usually around 0.1 - 0.2 up to 0.3 Å.

The three dimensional structure of a new crystal may be modeled using molecular replacement. The term "molecular replacement" refers to a method that involves generating a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning a molecule whose structure coordinates are known within the unit cell of the unknown crystal, so as best to account for the observed diffraction pattern of the unknown crystal. Phases may then be calculated from this model and combined with

the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. This, in turn, can be subject to any of the several forms of refinement to provide a final, accurate structure of the unknown crystal. Lattman, E., "Use of the Rotation and Translation Functions", in Methods in Enzymology, 115, pp. 55-77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", Int. Sci. Rev. Ser., No. 13, Gordon & Breach, New York, (1972).

Commonly used computer software packages for molecular replacement are CNX, X-PLOR (Brunger 1992, Nature 355: 472-475), AMoRE (Navaza, 1994, Acta Crystallogr. A50:157-163), the CCP4 package, the MERLOT package (P.M.D. Fitzgerald, J. Appl. Cryst., Vol. 21, pp. 273-278, 1988) and XTALVIEW (McCree et al (1992) J. Mol. Graphics 10: 44-46). The quality of the model may be analyzed using a program such as PROCHECK or 3D-Profiler (Laskowski et al 1993 J. Appl. Cryst. 26:283-291; Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991).

Homology modeling (also known as comparative modeling or knowledge-based modeling) methods may also be used to develop a three dimensional model from a polypeptide sequence based on the structures of known proteins. The method utilizes a computer model of a known protein, a computer representation of the amino acid sequence of the polypeptide with an unknown structure, and standard computer representations of the structures of amino acids. This method is well known to those skilled in the art (Greer, 1985, Science 228, 1055; Bundell et al 1988, Eur. J. Biochem. 172, 513; Knighton et al., 1992, Science 258:130-135, http://biochem.vt.edu/courses/-modeling/homology.htn). Computer programs that can be used in homology modeling are QUANTA and the Homology module in the Insight II modeling package distributed by Molecular Simulations Inc, or MODELLER (Rockefeller University, www.iucr.ac.uk/sinris-top/logical/prg-modeller.html).

Once a homology model has been generated it is analyzed to determine its correctness. A computer program available to assist in this analysis is the Protein Health module in QUANTA which provides a variety of tests. Other programs that provide structure analysis along with output include PROCHECK and 3D-Profiler (Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991). Once any irregularities have been resolved, the entire structure may be further refined.

Other molecular modeling techniques may also be employed in accordance with this invention. See, e.g., Cohen, N. C. *et al*, J. Med. Chem., 33, pp. 883-894 (1990). See also, Navix, M. A. and M. A. Marko, Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Under suitable circumstances, the entire process of solving a crystal structure may be accomplished in an automated fashion by a system such as ELVES (http://ucxray.berkeley.edu/~jamesh/elves/index.html) with little or no user intervention.

(ii) X-ray Structure

The present invention provides methods for determining some or all of the structural coordinates for amino acids of a polypeptide of the invention, or a complex thereof.

In another aspect, the present invention provides methods for identifying a druggable region of a polypeptide of the invention. For example, one such method includes: (a) obtaining crystals of a polypeptide of the invention or a fragment thereof such that the three dimensional structure of the crystallized protein can be determined to a resolution of 3.5 Å or better; (b) determining the three dimensional structure of the crystallized polypeptide or fragment using x-ray diffraction; and (c) identifying a druggable region of a polypeptide of the invention based on the three-dimensional structure of the polypeptide or fragment.

A three dimensional structure of a molecule or complex may be described by the set of atoms that best predict the observed diffraction data (that is, which possesses a minimal R value). Files may be created for the structure that defines each atom by its chemical identity, spatial coordinates in three dimensions, root mean squared deviation from the mean observed position and fractional occupancy of the observed position.

Those of skill in the art understand that a set of structure coordinates for an protein, complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations in the individual coordinates may have little affect on overall shape. Such variations in coordinates may be generated because of mathematical manipulations of the structure coordinates. For example, structure coordinates could be manipulated by crystallographic permutations of the structure coordinates, fractionalization of the structure coordinates, integer additions or subtractions to sets of the structure coordinates, inversion of the structure coordinates or any

combination of the above. Alternatively, modifications in the crystal structure due to mutations, additions, substitutions, and/or deletions of amino acids, or other changes in any of the components that make up the crystal, could also yield variations in structure coordinates. Such slight variations in the individual coordinates will have little affect on overall shape. If such variations are within an acceptable standard. error as compared to the original coordinates, the resulting three-dimensional shape is considered to be structurally equivalent. It should be noted that slight variations in individual structure coordinates of a polypeptide of the invention or a complex thereof would not be expected to significantly alter the nature of modulators that could associate with a druggable region thereof. Thus, for example, a modulator that bound to the active site of a polypeptide of the invention would also be expected to bind to or interfere with another active site whose structure coordinates define a shape that falls within the acceptable error.

A crystal structure of the present invention may be used to make a structural or computer model of the polypeptide, complex or portion thereof. A model may represent the secondary, tertiary and/or quaternary structure of the polypeptide, complex or portion. The configurations of points in space derived from structure coordinates according to the invention can be visualized as, for example, a holographic image, a stereodiagram, a model or a computer-displayed image, and the invention thus includes such images, diagrams or models.

(iii) Structural Equivalents

Various computational analyses can be used to determine whether a molecule or the active site portion thereof is structurally equivalent with respect to its three-dimensional structure, to all or part of a structure of a polypeptide of the invention or a portion thereof.

For the purpose of this invention, any molecule or complex or portion thereof, that has a root mean square deviation of conserved residue backbone atoms (N, Cα, C, O) of less than about 1.75 Å, when superimposed on the relevant backbone atoms described by the reference structure coordinates of a polypeptide of the invention, is considered "structurally equivalent" to the reference molecule. That is to say, the crystal structures of those portions of the two molecules are substantially identical, within acceptable error. Alternatively, the root mean square deviation may be is less than about 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å.

The term "root mean square deviation" is understood in the art and means the square root of the arithmetic mean of the squares of the deviations. It is a way to express the deviation or variation from a trend or object.

In another aspect, the present invention provides a scalable three-dimensional configuration of points, at least a portion of said points, and preferably all of said points, derived from structural coordinates of at least a portion of a polypeptide of the invention and having a root mean square deviation from the structure coordinates of the polypeptide of the invention of less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å. In certain embodiments, the portion of a polypeptide of the invention is 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the polypeptide.

In another aspect, the present invention provides a molecule or complex including a druggable region of a polypeptide of the invention, the druggable region being defined by a set of points having a root mean square deviation of less than about 1.75 Å from the structural coordinates for points representing (a) the backbone atoms of the amino acids contained in a druggable region of a polypeptide of the invention, (b) the side chain atoms (and optionally the Cα atoms) of the amino acids contained in such druggable region, or (c) all the atoms of the amino acids contained in such druggable region. In certain embodiments, only a portion of the amino acids of a druggable region may be included in the set of points, such as 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the druggable region. In certain embodiments, the root mean square deviation may be less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5, or 0.35 Å. In still other embodiments, instead of a druggable region, a stable domain, fragment or structural motif is used in place of a druggable region.

(iv) Machine Displays and Machine Readable Storage Media

The invention provides a machine-readable storage medium including a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, displays a graphical three-dimensional representation of any of the molecules or complexes, or portions thereof, of this invention. In another embodiment, the graphical three-dimensional representation of such molecule, complex or portion thereof includes the ± a root mean square deviation of certain atoms of such molecule by a specified amount, such as the backbone atoms by less than 0.8 Å. In another embodiment, a structural equivalent of such molecule, complex, or portion thereof, may be

displayed. In another embodiment, the portion may include a druggable region of the polypeptide of the invention.

According to one embodiment, the invention provides a computer for determining at least a portion of the structure coordinates corresponding to x-ray diffraction data obtained from a molecule or complex, wherein said computer includes: (a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates of a polypeptide of the invention; (b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises x-ray diffraction data from said molecule or complex; (c) a working memory for storing instructions for processing said machine-readable data of (a) and (b); (d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and (e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or complex. In certain embodiments, the structural coordinates displayed are structurally equivalent to the structural coordinates of a polypeptide of the invention.

In an alternative embodiment, the machine-readable data storage medium includes a data storage material encoded with a first set of machine readable data which includes the Fourier transform of the structure coordinates of a polypeptide of the invention or a portion thereof, and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data including the x-ray diffraction pattern of a molecule or complex to determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

For example, a system for reading a data storage medium may include a computer including a central processing unit ("CPU"), a working memory which may be, e.g., RAM (random access memory) or "core" memory, mass storage memory (such as one or more disk drives or CD-ROM drives), one or more display devices (e.g., cathode-ray tube ("CRT") displays, light emitting diode ("LED") displays, liquid crystal displays ("LCDs"), electroluminescent displays, vacuum fluorescent displays, field emission displays ("FEDs"), plasma displays, projection panels, etc.), one or more user input devices (e.g., keyboards, microphones, mice, touch screens, etc.), one or more input lines, and one or more output lines, all of which are interconnected by a conventional bidirectional system

bus. The system may be a stand-alone computer, or may be networked (e.g., through local area networks, wide area networks, intranets, extranets, or the internet) to other systems (e.g., computers, hosts, servers, etc.). The system may also include additional computer controlled devices such as consumer electronics and appliances.

Input hardware may be coupled to the computer by input lines and may be implemented in a variety of ways. Machine-readable data of this invention may be inputted via the use of a modem or modems connected by a telephone line or dedicated data line. Alternatively or additionally, the input hardware may include CD-ROM drives or disk drives. In conjunction with a display terminal, a keyboard may also be used as an input device.

Output hardware may be coupled to the computer by output lines and may similarly be implemented by conventional devices. By way of example, the output hardware may include a display device for displaying a graphical representation of an active site of this invention using a program such as QUANTA as described herein. Output hardware might also include a printer, so that hard copy output may be produced, or a disk drive, to store system output for later use.

In operation, a CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage devices, accesses to and from working memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention. Such programs are discussed in reference to the computational methods of drug discovery as described herein. References to components of the hardware system are included as appropriate throughout the following description of the data storage medium.

Machine-readable storage devices useful in the present invention include, but are not limited to, magnetic devices, electrical devices, optical devices, and combinations thereof. Examples of such data storage devices include, but are not limited to, hard disk devices, CD devices, digital video disk devices, floppy disk devices, removable hard disk devices, magneto-optic disk devices, magnetic tape devices, flash memory devices, bubble memory devices, holographic storage devices, and any other mass storage peripheral device. It should be understood that these storage devices include necessary hardware (e.g., drives, controllers, power supplies, etc.) as well as any necessary media (e.g., disks, flash cards, etc.) to enable the storage of data..

In one embodiment, the present invention contemplates a computer readable storage medium comprising structural data, wherein the data include the identity and three-dimensional coordinates of a polypeptide of the invention or portion thereof. In another aspect, the present invention contemplates a database comprising the identity and three-dimensional coordinates of a polypeptide of the invention or a portion thereof. Alternatively, the present invention contemplates a database comprising a portion or all of the atomic coordinates of a polypeptide of the invention or portion thereof.

(v) Structurally Similar Molecules and Complexes

Structural coordinates for a polypeptide of the invention can be used to aid in obtaining structural information about another molecule or complex. This method of the invention allows determination of at least a portion of the three-dimensional structure of molecules or molecular complexes which contain one or more structural features that are similar to structural features of a polypeptide of the invention. Similar structural features can include, for example, regions of amino acid identity, conserved active site or binding site motifs, and similarly arranged secondary structural elements (e.g., α helices and β sheets). Many of the methods described above for determining the structure of a polypeptide of the invention may be used for this purpose as well.

For the present invention, a "structural homolog" is a polypeptide that contains one or more amino acid substitutions, deletions, additions, or rearrangements with respect to the amino acid sequence of SEQ ID NO: 4 or other polypeptide of the invention, but that, when folded into its native conformation, exhibits or is reasonably expected to exhibit at least a portion of the tertiary (three-dimensional) structure of the polypeptide encoded by SEQ ID NO: 4 or such other polypeptide of the invention. For example, structurally homologous molecules can contain deletions or additions of one or more contiguous or noncontiguous amino acids, such as a loop or a domain. Structurally homologous molecules also include modified polypeptide molecules that have been chemically or enzymatically derivatized at one or more constituent amino acids, including side chain modifications, backbone modifications, and N- and C-terminal modifications including acetylation, hydroxylation, methylation, amidation, and the attachment of carbohydrate or lipid moieties, cofactors, and the like.

By using molecular replacement, all or part of the structure coordinates of a polypeptide of the invention can be used to determine the structure of a crystallized

molecule or complex whose structure is unknown more quickly and efficiently than attempting to determine such information *ab initio*. For example, in one embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a molecule or complex whose structure is unknown including: (a) crystallizing the molecule or complex of unknown structure; (b) generating an x-ray diffraction pattern from said crystallized molecule or complex; and (c) applying at least a portion of the structure coordinates for a polypeptide of the invention to the x-ray diffraction pattern to generate a three-dimensional electron density map of the molecule or complex whose structure is unknown.

In another aspect, the present invention provides a method for generating a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of a polypeptide of the invention within the unit cell of the crystal of the unknown molecule or complex so as best to account for the observed x-ray diffraction pattern of the crystal of the molecule or complex whose structure is unknown.

Structural information about a portion of any crystallized molecule or complex that is sufficiently structurally similar to a portion of a polypeptide of the invention may be resolved by this method. In addition to a molecule that shares one or more structural features with a polypeptide of the invention, a molecule that has similar bioactivity, such as the same catalytic activity, substrate specificity or ligand binding activity as a polypeptide of the invention, may also be sufficiently structurally similar to a polypeptide of the invention to permit use of the structure coordinates for a polypeptide of the invention to solve its crystal structure.

In another aspect, the method of molecular replacement is utilized to obtain structural information about complex containing a polypeptide of the invention, such as a complex between a modulator and a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof). In certain instances, the complex includes a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof) co-complexed with a modulator. For example, in one embodiment, the present invention contemplates a method for making a crystallized complex comprising a polypeptide of the invention, or a fragment thereof, and a compound having a molecular weight of less than 5 kDa, the method comprising: (a) crystallizing a polypeptide of the invention such that the crystals will diffract x-rays to a resolution of 3.5 Å or better; and (b) soaking the crystal in a solution

comprising the compound having a molecular weight of less than 5 kDa, thereby producing a crystallized complex comprising the polypeptide and the compound.

Using homology modeling, a computer model of a structural homolog or other polypeptide can be built or refined without crystallizing the molecule. For example, in another aspect, the present invention provides a computer-assisted method for homology modeling a structural homolog of a polypeptide of the invention including: aligning the amino acid sequence of a known or suspected structural homolog with the amino acid sequence of a polypeptide of the invention and incorporating the sequence of the homolog into a model of a polypeptide of the invention derived from atomic structure coordinates to yield a preliminary model of the homolog; subjecting the preliminary model to energy minimization to yield an energy minimized model; remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog.

In another embodiment, the present invention contemplates a method for determining the crystal structure of a homolog of a polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or equivalent thereof, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof; (b) obtaining crystals of a homologous polypeptide comprising an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 such that the three dimensional structure of the crystallized homologous polypeptide may be determined to a resolution of 3.5 Å or better; and (c) determining the three dimensional structure of the crystallized homologous polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a). In certain instances of the foregoing method, the atomic coordinates for the homologous polypeptide have a root mean square deviation from the backbone atoms of the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, of not more than 1.5 Å for all backbone atoms shared in common with the homologous polypeptide and the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof.

(vi) NMR Analysis Using X-ray Structural Data

In another aspect, the structural coordinates of a known crystal structure may be applied to nuclear magnetic resonance data to determine the three dimensional structures of

polypeptides with uncharacterized or incompletely characterized structure. (See for example, Wuthrich, 1986, John Wiley and Sons, New York: 176-199; Pflugrath et al., 1986, J. Molecular Biology 189: 383-386; Kline et al., 1986 J. Molecular Biology 189:377-382). While the secondary structure of a polypeptide may often be determined by NMR data, the spatial connections between individual pieces of secondary structure are not as readily determined. The structural coordinates of a polypeptide defined by x-ray crystallography can guide the NMR spectroscopist to an understanding of the spatial interactions between secondary structural elements in a polypeptide of related structure. Information on spatial interactions between secondary structural elements can greatly simplify NOE data from two-dimensional NMR experiments. In addition, applying the structural coordinates after the determination of secondary structure by NMR techniques simplifies the assignment of NOE's relating to particular amino acids in the polypeptide sequence.

In an embodiment, the invention relates to a method of determining three dimensional structures of polypeptides with unknown structures, by applying the structural coordinates of a crystal of the present invention to nuclear magnetic resonance data of the unknown structure. This method comprises the steps of: (a) determining the secondary structure of an unknown structure using NMR data; and (b) simplifying the assignment of through-space interactions of amino acids. The term "through-space interactions" defines the orientation of the secondary structural elements in the three dimensional structure and the distances between amino acids from different portions of the amino acid sequence. The term "assignment" defines a method of analyzing NMR data and identifying which amino acids give rise to signals in the NMR spectrum.

For all of this section on x-ray cystallography, see also Brooks et al. (1983) *J Comput Chem* 4:187-217; Weiner et al (1981) *J. Comput. Chem.* 106: 765; Eisenfield et al. (1991) *Am J Physiol* 261:C376-386; Lybrand (1991) *J Pharm Belg* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ Health Perspect* 61:185-190; and Kini et al. (1991) *J Biomol Struct Dyn* 9:475-488; Ryckaert et al. (1977) *J Comput Phys* 23:327; Van Gunsteren et al. (1977) *Mol Phys* 34:1311; Anderson (1983) *J Comput Phys* 52:24; J. Mol. Biol. 48: 442-453, 1970; Dayhoff et al., Meth. Enzymol. 91: 524-545, 1983; Henikoff and Henikoff, Proc. Nat. Acad. Sci. USA 89: 10915-10919, 1992; J. Mol. Biol. 233: 716-738, 1993; Methods in Enzymology, Volume 276, Macromolecular crystallography, Part A, ISBN 0-12-182177-3 and Volume 277, Macromolecular crystallography, Part B, ISBN 0-12-182178-1, Eds. Charles W.

Carter, Jr. and Robert M. Sweet (1997), Academic Press, Sàn Diego; Pfuetzner, et al., J. Biol. Chem. 272: 430-434 (1997).

6. Interacting Proteins

The present invention also provides methods for isolating specific protein interactors of a polypeptide of the invention, and complexes comprising a polypeptide of the invention and one or more interacting proteins. In one aspect, the present invention contemplates an isolated protein complex comprising a polypeptide of the invention and at least one protein that interacts with the polypeptide of the invention. The protein may be naturally-occurring. The interacting protein may be of *P. aeruginosa* origin. Alternatively, the interacting protein may be of mammalian origin or human origin. Either the polypeptide of the invention or the interacting protein or both may be a fusion protein.

The present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention or a fragment thereof, the method comprising: (a) exposing a sample to a solid substrate coupled to a polypeptide of the invention or a fragment thereof under conditions which promote protein-protein interactions; (b) washing the solid substrate so as to remove any polypeptides interacting non-specifically with the polypeptide or fragment; (c) eluting the polypeptides which specifically interact with the polypeptide or fragment; and (d) identifying the interacting protein. The sample may be an extract of *P. aeruginosa*, a mammalian cell extract, a human cell extract, a purified protein (or a fragment thereof), or a mixture of purified proteins (or fragments thereof). The interacting protein may be identified by a number of methods, including mass spectrometry or protein sequencing.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of present invention or a fragment thereof, the method comprising: (a) subjecting a sample to protein-affinity chromatography on multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) separating the components to isolate a polypeptide capable of interacting with the polypeptide or fragment; and (c) analyzing the interacting protein by mass spectrometry to identify the interacting protein. In certain instances, the foregoing method will use polyacrylamide gel electrophoresis without SDS.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention, the method comprising: (a) subjecting a cellular extract or extracellular fluid to protein-affinity chromatography on multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) gel-separating the components to isolate an interacting protein; wherein the interacting protein is observed to vary in amount in direct relation to the concentration of coupled polypeptide or fragment; (c) digesting the interacting protein to give corresponding peptides; (d) analyzing the peptides by MALDI-TOF mass spectrometry or post source decay to determine the peptide masses; and (d) performing correlative database searches with the peptide, or peptide fragment, masses, whereby the interacting protein is identified based on the masses of the peptides or peptide fragments. The foregoing method may include the further step of including the identifies of any interacting proteins into a relational database.

In another aspect, the invention further contemplates a method for identifying modulators of a protein complex, the method comprising: (a) contacting a protein complex comprising a polypeptide of the invention and an interacting protein with one or more test compounds; and (b) determining the effect of the test compound on (i) the activity of the protein complex, (ii) the amount of the protein complex, (iii) the stability of the protein complex, (iv) the conformation of the protein complex, (v) the activity of at least one polypeptide included in the protein complex, (vi) the conformation of at least one polypeptide included in the protein complex, (vii) the intracellular localization of the protein complex or a component thereof, (viii) the transcription level of a gene dependent on the complex, and/or (ix) the level of second messenger levels in a cell; thereby identifying modulators of the protein complex. The foregoing method may be carried out *in vitro* or *in vivo* as appropriate.

Typically, it will be desirable to immobilize a polypeptide of the invention to facilitate separation of complexes comprising a polypeptide of the invention from uncomplexed forms of the interacting proteins, as well as to accommodate automation of the assay. The polypeptide of the invention, or ligand, may be immobilized onto a solid support (e.g., column matrix, microtiter plate, slide, etc.). In certain embodiments, the ligand may be purified. In certain instances, a fusion protein may be provided which adds a domain that permits the ligand to be bound to a support.

In various *in vitro* embodiments, the set of proteins engaged in a protein-protein interaction comprises a cell extract, a clarified cell extract, or a reconstituted protein mixture of at least semi-purified proteins. By semi-purified, it is meant that the proteins utilized in the reconstituted mixture have been previously separated from other cellular or viral proteins. For instance, in contrast to cell lysates, the proteins involved in a protein-protein interaction are present in the mixture to at least about 50% purity relative to all other proteins in the mixture, and more preferably are present in greater, even 90-95%, purity. In certain embodiments of the subject method, the reconstituted protein mixture is derived by mixing highly purified proteins such that the reconstituted mixture substantially lacks other proteins (such as of cellular or viral origin) which might interfere with or otherwise alter the ability to measure activity resulting from the given protein-protein interaction.

Complex formation involving a polypeptide of the invention and another component polypeptide or a substrate polypeptide, may be detected by a variety of techniques. For instance, modulation in the formation of complexes can be quantitated using, for example, detectably labeled proteins (e.g. radiolabeled, fluorescently labeled, or enzymatically labeled), by immunoassay, or by chromatographic detection.

The present invention also provides assays for identifying molecules which are modulators of a protein-protein interaction involving a polypeptide of the invention, or are a modulator of the role of the complex comprising a polypeptide of the invention in the infectivity or pathogenicity of *P. aeruginosa*. In one embodiment, the assay detects agents which inhibit formation or stabilization of a protein complex comprising a polypeptide of the invention and one or more additional proteins. In another embodiment, the assay detects agents which modulate the intrinsic biological activity of a protein complex comprising a polypeptide of the invention, such as an enzymatic activity, binding to other cellular components, cellular compartmentalization, signal transduction, and the like. Such modulators may be used, for example, in the treatment of *P. aeruginosa* related diseases or disorders. In certain embodiments, the compound is a mechanism based inhibitor which chemically alters one member of a protein-protein interaction involving a polypeptide of the invention and which is a specific inhibitor of that member, e.g. has an inhibition constant about 10-fold, 100-fold, or 1000-fold different compared to homologous proteins.

In one embodiment, proteins that interact with a polypeptide of the invention may be isolated using immunoprecipitation. A polypeptide of the invention may be expressed in

P. aeruginosa, or in a heterologous system. The cells expressing a polypeptide of the invention are then lysed under conditions which maintain protein-protein interactions, and complexes comprising a polypeptide of the invention are isolated. For example, a polypeptide of the invention may be expressed in mammalian cells, including human cells, in order to identify mammalian proteins that interact with a polypeptide of the invention and therefore may play a role in *P. aeruginosa* infectivity or proliferation. In one embodiment, a polypeptide of the invention is expressed in the cell type for which it is desirable to find interacting proteins. For example, a polypeptide of the invention may be expressed in *P. aeruginosa* in order to find *P. aeruginosa* derived interacting proteins.

In an alternative embodiment, a polypeptide of the invention is expressed and purified and then mixed with a potential interacting protein or mixture of proteins to identify complex formation. The potential interacting protein may be a single purified or semi-purified protein, or a mixture of proteins, including a mixture of purified or semi-purified proteins, a cell lysate, a clarified cell lysate, a semi-purified cell lysate, etc.

In certain embodiments, it may be desirable to use a tagged version of a polypeptide of the invention in order to facilitate isolation of complexes from the reaction mixture. Suitable tags for immunoprecipitation experiments include HA, myc, FLAG, HIS, GST, protein A, protein G, etc. Immunoprecipitation from a cell lysate or other protein mixture may be carried out using an antibody specific for a polypeptide of the invention or using an antibody which recognizes a tag to which a polypeptide of the invention is fused (e.g., anti-HA, anti-myc, anti-FLAG, etc.). Antibodies specific for a variety of tags are known to the skilled artisan and are commercially available from a number of sources. In the case where a polypeptide of the invention is fused to a His, GST, or protein A/G tag, immunoprecipitation may be carried out using the appropriate affinity resin (e.g., beads functionalized with Ni, glutathione, Fc region of IgG, etc.). Test compounds which modulate a protein-protein interaction involving a polypeptide of the invention may be identified by carrying out the immunoprecipitation reaction in the presence and absence of the test agent and comparing the level and/or activity of the protein complex between the two reactions.

In another embodiment, proteins that interact with a polypeptide of the invention may be identified using affinity chromatography. Some examples of such chromatography are described in USSN 09/727,812, filed November 30, 2000, and the PCT Application

filed November 30, 2001 and entitled "Methods for Systematic Identification of Protein-Protein Interactions and other Properties", which claims priority to such U.S. application.

In one aspect, for affinity chromatography using a solid support, a polypeptide of the invention or a fragment thereof may be attached by a variety of means known to those of skill in the art. For example, the polypeptide may be coupled directly (through a covalent linkage) to commercially available pre-activated resins as described in Formosa et al., Methods in Enzymology 1991, 208, 24-45; Sopta et al, J. Biol. Chem. 1985, 260, 10353-60; Archambault et al., Proc. Natl. Acad. Sci. USA 1997, 94, 14300-5. Alternatively, the polypeptide may be tethered to the solid support through high affinity binding interactions. If the polypeptide is expressed fused to a tag, such as GST, the fusion tag can be used to anchor the polypeptide to the matrix support, for example Sepharose beads containing immobilized glutathione. Solid supports that take advantage of these tags are commercially available.

In another aspect, the support to which a polypeptide may be immobilized is a soluble support, which may facilitate certain steps performed in the methods of the present invention. For example, the soluble support may be soluble in the conditions employed to create a binding interaction between a target and the polypeptide, and then used under conditions in which it is a solid for elution of the proteins or other biological materials that bind to a polypeptide.

The concentration of the coupled polypeptide may have an affect on the sensitivity of the method. In certain embodiments, to detect interactions most efficiently, the concentration of the polypeptide bound to the matrix should be at least 10-fold higher than the K_d of the interaction. Thus, the concentration of the polypeptide bound to the matrix should be highest for the detection of the weakest protein-protein interactions. However, if the concentration of the immobilized polypeptide is not as high as may be ideal, it may still be possible to observe protein-protein interactions of interest by, for example, increasing the concentration of the polypeptide or other moiety that interacts with the coupled polypeptide. The level of detection will of course vary with each different polypeptide, interactor, conditions of the assay, etc. In certain instances, the interacting protein binds to the polypeptide with a K_d of about 10^{-5} M to about 10^{-8} M or 10^{-10} M.

In another aspect, the coupling may be done at various ratios of the polypeptide to the resin. An upper limit of the protein : resin ratio may be determined by the isoelectric

point and the ionic nature of the protein, although it may be possible to achieve higher polypeptide concentrations by use of various methods.

In certain embodiments, several concentrations of the polypeptide immobilized on a solid or soluble support may be used. One advantage of using multiple concentrations, although not a requirement, is that one may be able to obtain an estimate for the strength of the protein-protein interaction that is observed in the affinity chromatography experiment. Another advantage of using multiple concentrations is that a binding curve which has the proper shape may indicate that the interaction that is observed is biologically important rather than a spurious interaction with denatured protein.

In one example of such an embodiment, a series of columns may be prepared with varying concentrations of polypeptide (mg polypeptide/ml resin volume). The number of columns employed may be between 2 to 8, 10, 12, 15, 25 or more, each with a different concentration of attached polypeptide. Larger numbers of columns may be used if appropriate for the polypeptide being examined, and multiple columns may be used with the same concentration as any methods may require. In certain embodiments, 4 to 6 columns are prepared with varying concentrations of polypeptide. In another aspect of this embodiment, two control columns may be prepared: one that contains no polypeptide and a second that contains the highest concentration of polypeptide but is not treated with extract. After elution of the columns and separation of the eluent components (by one of the methods described below), it may be possible to distinguish the interacting proteins (if any) from the non-specific bound proteins as follows. The concentration of the interacting proteins, as determined by the intensity of the band on the gel, will increase proportionally to the increase in polypeptide concentration but will be missing from the second control column. This allows for the identification of unknown interacting proteins.

The method of the invention may be used for small-scale analysis. A variety of column sizes, types, and geometries may be used. In addition, other vessel shapes and sizes having a smaller scale than is usually found in laboratory experiments may be used as well, including a plurality of wells in a plate. For high throughput analysis, it is advantageous to use small volumes, from about 20, 30, 50, 80 or 100 µl. Larger or small volumes may be used, as necessary, and it may be possible to achieve high throughput analysis using them. The entire affinity chromatography procedure may be automated by assembling the micro-columns into an array (e.g. with 96 micro-column arrays).

A variety of materials may be used as the source of potential interacting proteins. In one embodiment, a cellular extract or extracellular fluid may be used. The choice of starting material for the extract may be based upon the cell or tissue type or type of fluid that would be expected to contain proteins that interact with the target protein. Micro-organisms or other organisms are grown in a medium that is appropriate for that organism and can be grown in specific conditions to promote the expression of proteins that may interact with the target protein. Exemplary starting material that may be used to make a suitable extract are: 1) one or more types of tissue derived from an animal, plant, or other multi-cellular organism, 2) cells grown in tissue culture that were derived from an animal or human, plant or other source, 3) micro-organisms grown in suspension or non-suspension cultures, 4) virus-infected cells, 5) purified organelles (including, but not restricted to nuclei, mitochondria, membranes, Golgi, endoplasmic reticulum, lysosomes, or peroxisomes) prepared by differential centrifugation or another procedure from animal, plant or other kinds of eukaryotic cells, 6) serum or other bodily fluids including, but not limited to, blood, urine, semen, synovial fluid, cerebrospinal fluid, amniotic fluid, lymphatic fluid or interstitial fluid. In other embodiments, a total cell extract may not be the optimal source of interacting proteins. For example, if the ligand is known to act in the nucleus, a nuclear extract can provide a 10-fold enrichment of proteins that are likely to interact with the ligand. In addition, proteins that are present in the extract in low concentrations may be enriched using another chromatographic method to fractionate the extract before screening various pools for an interacting protein.

Extracts are prepared by methods known to those of skill in the art. The extracts may be prepared at a low temperature (e.g., 4°C) in order to retard denaturation or degradation of proteins in the extract. The pH of the extract may be adjusted to be appropriate for the body fluid or tissue, cellular, or organellar source that is used for the procedure (e.g. pH 7-8 for cytosolic extracts from mammals, but low pH for lysosomal extracts). The concentration of chaotropic or non-chaotropic salts in the extracting solution may be adjusted so as to extract the appropriate sets of proteins for the procedure. Glycerol may be added to the extract, as it aids in maintaining the stability of many proteins and also reduces background non-specific binding. Both the lysis buffer and column buffer may contain protease inhibitors to minimize proteolytic degradation of proteins in the extract and to protect the polypeptide. Appropriate co-factors that could potentially interact with the interacting proteins may be added to the extracting solution. One or more nucleases or

another reagent may be added to the extract, if appropriate, to prevent protein-protein interactions that are mediated by nucleic acids. Appropriate detergents or other agents may be added to the solution, if desired, to extract membrane proteins from the cells or tissue. A reducing agent (e.g. dithiothreitol or 2-mercaptoethanol or glutathione or other agent) may be added. Trace metals or a chelating agent may be added, if desired, to the extracting solution.

Usually, the extract is centrifuged in a centrifuge or ultracentrifuge or filtered to provide a clarified supernatant solution. This supernatant solution may be dialyzed using dialysis tubing, or another kind of device that is standard in the art, against a solution that is similar to, but may not be identical with, the solution that was used to make the extract. The extract is clarified by centrifugation or filtration again immediately prior to its use in affinity chromatography.

In some cases, the crude lysate will contain small molecules that can interfere with the affinity chromatography. This can be remedied by precipitating proteins with ammonium sulfate, centrifugation of the precipitate, and re-suspending the proteins in the affinity column buffer followed by dialysis. An additional centrifugation of the sample may be needed to remove any particulate matter prior to application to the affinity columns.

The amount of cell extract applied to the column may be important for any embodiment. If too little extract is applied to the column and the interacting protein is present at low concentration, the level of interacting protein retained by the column may be difficult to detect. Conversely, if too much extract is applied to the column, protein may precipitate on the column or competition by abundant interacting proteins for the limited amount of protein ligand may result in a difficulty in detecting minor species.

The columns functionalized with a polypeptide of the invention are loaded with protein extract from an appropriate source that has been dialyzed against a buffer that is consistent with the nature of the expected interaction. The pH, salt concentrations and the presence or absence of reducing and chelating agents, trace metals, detergents, and co-factors may be adjusted according to the nature of the expected interaction. Most commonly, the pH and the ionic strength are chosen so as to be close to physiological for the source of the extract. The extract is most commonly loaded under gravity onto the columns at a flow rate of about 4-6 column volumes per hour, but this flow rate can be adjusted for particular circumstances in an automated procedure.

The volume of the extract that is loaded on the columns can be varied but is most commonly equivalent to about 5 to 10 column volumes. When large volumes of extract are loaded on the columns, there is often an improvement in the signal-to-noise ratio because more protein from the extract is available to bind to the protein ligand, whereas the background binding of proteins from the extract to the solid support saturates with low amounts of extract.

A control column may be included that contains the highest concentration of protein ligand, but buffer rather than extract is loaded onto this column. The elutions (eluates) from this column will contain polypeptide that failed to be attached to the column in a covalent manner, but no proteins that are derived from the extract.

The columns may be washed with a buffer appropriate to the nature of the interaction being analyzed, usually, but not necessarily, the same as the loading buffer. An elution buffer with an appropriate pH, glycerol, and the presence or absence of reducing agent, chelating agent, cofactors, and detergents are all important considerations. The columns may be washed with anywhere from about 5 to 20 column volumes of each wash buffer to eliminate unbound proteins from the natural extract. The flow rate of the wash is usually adjusted to about 4 to 6 column volumes per hour by using gravity or an automated procedure, but other flow rates are possible in specific circumstances.

In order to elute the proteins that have been retained by the column, the interactions between the extract proteins and the column ligand should be disrupted. This is performed by eluting the column with a solution of salt or detergent. Retention of activity by the eluted proteins may require the presence of glycerol and a buffer of appropriate pH, as well as proper choices of ionic strength and the presence or absence of appropriate reducing agent, chelating agent, trace metals, cofactors, detergents, chaotropic agents, and other reagents. If physical identification of the bound proteins is the objective, the elution may be performed sequentially, first with buffer of high ionic strength and then with buffer containing a protein denaturant, most commonly, but not restricted to sodium dodecyl sulfate (SDS), urea, or guanidine hydrochloride. In certain instances, the column is eluted with a protein denaturant, particularly SDS, for example as a 1% SDS solution. Using only the SDS wash, and omitting the salt wash, may result in SDS-gels that have higher resolution (sharper bands with less smearing). Also, using only the SDS wash results in half as many samples to analyze. The volume of the eluting solution may be varied but is normally about 2 to 4 column volumes. For 20 ml columns, the flow rate of the eluting

procedures are most commonly about 4 to 6 column volumes per hour, under gravity, but can be varied in an automated procedure.

The proteins from the extract that were bound to and are eluted from the affinity columns may be most easily resolved for identification by an electrophoresis procedure, but this procedure may be modified, replaced by another suitable method, or omitted. Any of the denaturing or non-denaturing electrophoresis procedures that are standard in the art may be used for this purpose, including SDS-PAGE, gradient gels, capillary electrophoresis, and two-dimensional gels with isoelectric focusing in the first dimension and SDS-PAGE in the second. Typically, the individual components in the column eluent are separated by polyacrylamide gel electrophoresis.

After electrophoresis, protein bands or spots may be visualized using any number of methods know to those of skill in the art, including staining techniques such as Coomassie blue or silver staining, or some other agent that is standard in the art. Alternatively, autoradiography can be used for visualizing proteins isolated from organisms cultured on media containing a radioactive label, for example $^{35}SO_4^{2-}$ or ^{35}[S]methionine, that is incorporated into the proteins. The use of radioactively labeled extract allows a distinction to be made between extract proteins that were retained by the column and proteolytic fragments of the ligand that may be released from the column.

Protein bands that are derived from the extract (i.e. it did not elute from the control column that was not loaded with protein from the extract) and bound to an experimental column that contained polypeptide covalently attached to the solid support, and did not bind to a control column that did not contain any polypeptide, may be excised from the stained electrophoretic gel and further characterized.

To identify the protein interactor by mass spectrometry, it may be desirable to reduce the disulfide bonds of the protein followed by alkylation of the free thiols prior to digestion of the protein with protease. The reduction may be performed by treatment of the gel slice with a reducing agent, for example with dithiothreitol, whereupon, the protein is alkylated by treating the gel slice with a suitable alkylating agent, for example iodoacetamide.

Prior to analysis by mass spectrometry, the protein may be chemically or enzymatically digested. The protein sample in the gel slice may be subjected to *in-gel* digestion. Shevchenko A. et al., Mass Spectrometric Sequencing of Proteins from Silver

Stained Polyacrylamide Gels. Analytical Chemistry 1996, 58, 850-858. One method of digestion is by treatment with the enzyme trypsin. The resulting peptides are extracted from the gel slice into a buffer.

The peptide fragments may be purified, for example by use of chromatography. A solid support that differentially binds the peptides and not the other compounds derived from the gel slice, the protease reaction or the peptide extract may be used. The peptides may be eluted from the solid support into a small volume of a solution that is compatible with mass spectrometry (e.g. 50% acetonitrile/0.1% trifluoroacetic acid).

The preparation of a protein sample from a gel slice that is suitable for mass spectrometry may also be done by an automated procedure.

Peptide samples derived from gel slices may be analyzed by any one of a variety of techniques in mass spectrometry as further described above. This technique may be used to assign function to an unknown protein based upon the known function of the interacting protein in the same or a homologous/orthologous organism.

Eluates from the affinity chromatography columns may also be analyzed directly without resolution by electrophoretic methods, by proteolytic digestion with a protease in solution, followed by applying the proteolytic digestion products to a reverse phase column and eluting the peptides from the column.

In yet another embodiment, proteins that interact with a polypeptide of the invention may be identified using an interaction trap assay (see also, U.S. Patent NO: 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J Biol Chem* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; and Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696).

In another embodiment, a method of the present invention makes use of chimeric genes which express hybrid proteins. To illustrate, a first hybrid gene comprises the coding sequence for a DNA-binding domain of a transcriptional activator fused in frame to the coding sequence for a "bait" protein, e.g., a polypeptide of the invention of sufficient length to bind to a potential interacting protein. The second hybrid protein encodes a transcriptional activation domain fused in frame to a gene encoding a "fish" protein, e.g., a potential interacting protein of sufficient length to interact with a polypeptide of the invention portion of the bait fusion protein. If the bait and fish proteins are able to interact, e.g., form a protein-protein interaction, they bring into close proximity the two domains of

the transcriptional activator. This proximity causes transcription of a reporter gene which is operably linked to a transcriptional regulatory site responsive to the transcriptional activator, and expression of the reporter gene can be detected and used to score for the interaction of the bait and fish proteins.

In accordance with the present invention, the method includes providing a host cell, typically a yeast cell, e.g., *Kluyverei lactis, Schizosaccharomyces pombe, Ustilago maydis, Saccharomyces cerevisiae, Neurospora crassa, Aspergillus niger, Aspergillus nidulans, Pichia pastoris, Candida tropicalis, and Hansenula polymorpha*, though most preferably *S cerevisiae* or *S. pombe*. The host cell contains a reporter gene having a binding site for the DNA-binding domain of a transcriptional activator used in the bait protein, such that the reporter gene expresses a detectable gene product when the gene is transcriptionally activated. The first chimeric gene may be present in a chromosome of the host cell, or as part of an expression vector.

The host cell also contains a first chimeric gene which is capable of being expressed in the host cell. The gene encodes a chimeric protein, which comprises (a) a DNA-binding domain that recognizes the responsive element on the reporter gene in the host cell, and (b) a bait protein (e.g., a polypeptide of the invention).

A second chimeric gene is also provided which is capable of being expressed in the host cell, and encodes the "fish" fusion protein. In one embodiment, both the first and the second chimeric genes are introduced into the host cell in the form of plasmids. Preferably, however, the first chimeric gene is present in a chromosome of the host cell and the second chimeric gene is introduced into the host cell as part of a plasmid.

The DNA-binding domain of the first hybrid protein and the transcriptional activation domain of the second hybrid protein may be derived from transcriptional activators having separable DNA-binding and transcriptional activation domains. For instance, these separate DNA-binding and transcriptional activation domains are known to be found in the yeast GAL4 protein, and are known to be found in the yeast GCN4 and ADR1 proteins. Many other proteins involved in transcription also have separable binding and transcriptional activation domains which make them useful for the present invention, and include, for example, the LexA and VP16 proteins. It will be understood that other (substantially) transcriptionally-inert DNA-binding domains may be used in the subject constructs; such as domains of ACE1, λcI, lac repressor, jun or fos. In another

embodiment, the DNA-binding domain and the transcriptional activation domain may be from different proteins. The use of a LexA DNA binding domain provides certain advantages. For example, in yeast, the LexA moiety contains no activation function and has no known affect on transcription of yeast genes. In addition, use of LexA allows control over the sensitivity of the assay to the level of interaction (see, for example, the Brent *et al.* PCT publication WO94/10300).

In certain embodiments, any enzymatic activity associated with the bait or fish proteins is inactivated, e.g., dominant negative or other mutants of a protein-protein interaction component can be used.

Continuing with the illustrative example, a polypeptide of the invention-mediated interaction, if any, between the bait and fish fusion proteins in the host cell, causes the activation domain to activate transcription of the reporter gene. The method is carried out by introducing the first chimeric gene and the second chimeric gene into the host cell, and subjecting that cell to conditions under which the bait and fish fusion proteins and are expressed in sufficient quantity for the reporter gene to be activated. The formation of a protein complex containing a polypeptide of the invention results in a detectable signal produced by the expression of the reporter gene.

In still further embodiments, the protein-protein interaction of interest is generated in whole cells, taking advantage of cell culture techniques to support the subject assay. For example, the protein-protein interaction of interest can be constituted in a prokaryotic or eukaryotic cell culture system. Advantages to generating the protein complex in an intact cell includes the ability to screen for inhibitors of the level or activity of the complex which are functional in an environment more closely approximating that which therapeutic use of the inhibitor would require, including the ability of the agent to gain entry into the cell. Furthermore, certain of the *in vivo* embodiments of the assay are amenable to high through-put analysis of candidate agents.

The components of the protein complex comprising a polypeptide of the invention can be endogenous to the cell selected to support the assay. Alternatively, some or all of the components can be derived from exogenous sources. For instance, fusion proteins can be introduced into the cell by recombinant techniques (such as through the use of an expression vector), as well as by microinjecting the fusion protein itself or mRNA encoding the fusion protein. Moreover, in the whole cell embodiments of the subject assay, the

reporter gene construct can provide, upon expression, a selectable marker. Such embodiments of the subject assay are particularly amenable to high through-put analysis in that proliferation of the cell can provide a simple measure of the protein-protein interaction.

The amount of transcription from the reporter gene may be measured using any method known to those of skill in the art to be suitable. For example, specific mRNA expression may be detected using Northern blots or specific protein product may be identified by a characteristic stain, western blots or an intrinsic activity. In certain embodiments, the product of the reporter gene is detected by an intrinsic activity associated with that product. For instance, the reporter gene may encode a gene product that, by enzymatic activity, gives rise to a detection signal based on color, fluorescence, or luminescence.

The interaction trap assay of the invention may also be used to identify test agents capable of modulating formation of a complex comprising a polypeptide of the invention. In general, the amount of expression from the reporter gene in the presence of the test compound is compared to the amount of expression in the same cell in the absence of the test compound. Alternatively, the amount of expression from the reporter gene in the presence of the test compound may be compared with the amount of transcription in a substantially identical cell that lacks a component of the protein-protein interaction involving a polypeptide of the invention.

7. Antibodies

Another aspect of the invention pertains to antibodies specifically reactive with a polypeptide of the invention. For example, by using peptides based on a polypeptide of the invention, e.g., having an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 or an immunogenic fragment thereof, antisera or monoclonal antibodies may be made using standard methods. An exemplary immunogenic fragment may contain eight, ten or more consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4. Certain fragments that are predicted to be immunogenic for the subject amino acid sequences (predicted) are set forth in Table 2 contained in FIGURE 7.

The term "antibody" as used herein is intended to include fragments thereof which are also specifically reactive with a polypeptide of the invention. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the

same manner as is suitable for whole antibodies. For example, $F(ab')_2$ fragments can be generated by treating antibody with pepsin. The resulting $F(ab')_2$ fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules, as well as single chain (scFv) antibodies. Also within the scope of the invention are trimeric antibodies, humanized antibodies, human antibodies, and single chain antibodies. All of these modified forms of antibodies as well as fragments of antibodies are intended to be included in the term "antibody".

In one aspect, the present invention contemplates a purified antibody that binds specifically to a polypeptide of the invention and which does not substantially cross-react with a protein which is less than about 80%, or less than about 90%, identical to SEQ ID NO: 2 or SEQ ID NO: 4. In another aspect, the present invention contemplates an array comprising a substrate having a plurality of address, wherein at least one of the addresses has disposed thereon a purified antibody that binds specifically to a polypeptide of the invention.

Antibodies may be elicited by methods known in the art. For example, a mammal such as a mouse, a hamster or rabbit may be immunized with an immunogenic form of a polypeptide of the invention (e.g., an antigenic fragment which is capable of eliciting an antibody response). Alternatively, immunization may occur by using a nucleic acid of the acid, which presumably *in vivo* expresses the polypeptide of the invention giving rise to the immunogenic response observed. Techniques for conferring immunogenicity on a protein or peptide include conjugation to carriers or other techniques well known in the art. For instance, a peptidyl portion of a polypeptide of the invention may be administered in the presence of adjuvant. The progress of immunization may be monitored by detection of antibody titers in plasma or serum. Standard ELISA or other immunoassays may be used with the immunogen as antigen to assess the levels of antibodies.

Following immunization, antisera reactive with a polypeptide of the invention may be obtained and, if desired, polyclonal antibodies isolated from the serum. To produce monoclonal antibodies, antibody producing cells (lymphocytes) may be harvested from an immunized animal and fused by standard somatic cell fusion procedures with immortalizing cells such as myeloma cells to yield hybridoma cells. Such techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler

and Milstein, (1975) *Nature*, 256: 495-497), as the human B cell hybridoma technique (Kozbar et al., (1983) *Immunology Today*, 4: 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. pp. 77-96). Hybridoma cells can be screened immunochemically for production of antibodies specifically reactive with the polypeptides of the invention and the monoclonal antibodies isolated.

Antibodies directed against the polypeptides of the invention can be used to selectively block the action of the polypeptides of the invention. Antibodies against a polypeptide of the invention may be employed to treat infections, particularly bacterial infections and diseases. For example, the present invention contemplates a method for treating a subject suffering from a *P. aeruginosa* related disease or disorder, comprising administering to an animal having the condition a therapeutically effective amount of a purified antibody that binds specifically to a polypeptide of the invention. In another example, the present invention contemplates a method for inhibiting SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *P. aeruginosa*, comprising contacting *P. aeruginosa* with a purified antibody that binds specifically to a polypeptide of the invention.

In one embodiment, antibodies reactive with a polypeptide of the invention are used in the immunological screening of cDNA libraries constructed in expression vectors, such as λgt11, λgt18-23, λZAP, and λORF8. Messenger libraries of this type, having coding sequences inserted in the correct reading frame and orientation, can produce fusion proteins. For instance, λgt11 will produce fusion proteins whose amino termini consist of ß-galactosidase amino acid sequences and whose carboxy termini consist of a foreign polypeptide. Antigenic epitopes of a polypeptide of the invention can then be detected with antibodies, as, for example, reacting nitrocellulose filters lifted from phage infected bacterial plates with an antibody specific for a polypeptide of the invention. Phage scored by this assay can then be isolated from the infected plate. Thus, homologs of a polypeptide of the invention can be detected and cloned from other sources.

Antibodies may be employed to isolate or to identify clones expressing the polypeptides to purify the polypeptides by affinity chromatography.

In other embodiments, the polypeptides of the invention may be modified so as to increase their immunogenicity. For example, a polypeptide, such as an antigenically or

immunologically equivalent derivative, may be associated, for example by conjugation, with an immunogenic carrier protein for example bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH). Alternatively a multiple antigenic peptide comprising multiple copies of the protein or polypeptide, or an antigenically or immunologically equivalent polypeptide thereof may be sufficiently antigenic to improve immunogenicity so as to obviate the use of a carrier.

In other embodiments, the antibodies of the invention, or variants thereof, are modified to make them less immunogenic when administered to a subject. For example, if the subject is human, the antibody may be "humanized"; where the complimentarity determining region(s) of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in Jones, P. et al. (1986), Nature 321, 522-525 or Tempest et al. (1991) Biotechnology 9, 266-273. Also, transgenic mice, or other mammals, may be used to express humanized antibodies. Such humanization may be partial or complete.

The use of a nucleic acid of the invention in genetic immunization may employ a suitable delivery method such as direct injection of plasmid DNA into muscles (Wolff et al., Hum Mol Genet 1992, 1:363, Manthorpe et al., Hum. Gene Ther. 1963:4, 419), delivery of DNA complexed with specific protein carriers (Wu et al., J Biol Chem. 1989: 264,16985), coprecipitation of DNA with calcium phosphate (Benvenisty & Reshef, PNAS USA, 1986:83,9551), encapsulation of DNA in various forms of liposomes (Kaneda et al., Science 1989:243,375), particle bombardment (Tang et al., Nature 1992, 356:152, Eisenbraun et al., DNA Cell Biol 1993, 12:791) and *in vivo* infection using cloned retroviral vectors (Seeger et al., PNAS USA 1984:81,5849).

8. Diagnostic Assays

The invention further provides a method for detecting the presence of *P. aeruginosa* in a biological sample. Detection of *P. aeruginosa* in a subject, particularly a mammal, and especially a human, will provide a diagnostic method for diagnosis of a *P. aeruginosa* related disease or disorder. In general, the method involves contacting the biological sample with a compound or an agent capable of detecting a polypeptide of the invention or a nucleic acid of the invention. The term "biological sample" when used in reference to a

diagnostic assay is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The detection method of the invention may be used to detect the presence of *P. aeruginosa* in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of a nucleic acid of the invention include Northern hybridizations and in situ hybridizations. *In vitro* techniques for detection of polypeptides of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunofluorescence, radioimmunoassays and competitive binding assays. Alternatively, polypeptides of the invention can be detected *in vivo* in a subject by introducing into the subject a labeled antibody specific for a polypeptide of the invention. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. It may be possible to use all of the diagnostic methods disclosed herein for pathogens in addition to *P. aeruginosa*.

Nucleic acids for diagnosis may be obtained from an infected individual's cells and tissues, such as bone, blood, muscle, cartilage, and skin. Nucleic acids, e.g., DNA and RNA, may be used directly for detection or may be amplified, e.g., enzymatically by using PCR or other amplification technique, prior to analysis. Using amplification, characterization of the species and strain of prokaryote present in an individual, may be made by an analysis of the genotype of the prokaryote gene. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the genotype of a reference sequence. Point mutations can be identified by hybridizing a nucleic acid, e.g., amplified DNA, to a nucleic acid of the invention, which nucleic acid may be labeled. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in the electrophoretic mobility of the DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing. See, e.g. Myers et al., Science, 230: 1242 (1985). Sequence changes at specific locations also may be revealed by nuclease protection assays, such as RNase and S1 protection or a chemical cleavage method. See, e.g., Cotton et al., Proc. Natl. Acad. Sci., USA, 85: 4397-4401 (1985).

Agents for detecting a nucleic acid of the invention, e.g., comprising the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3, include labeled or labelable nucleic acid probes capable of hybridizing to a nucleic acid of the invention. The nucleic acid probe can

comprise, for example, the full length sequence of a nucleic acid of the invention, or an equivalent thereof, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. Agents for detecting a polypeptide of the invention, e.g., comprising an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, include labeled or labelable antibodies capable of binding to a polypeptide of the invention. Antibodies may be polyclonal, or alternatively, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or $F(ab')_2$) can be used. Labeling the probe or antibody also encompasses direct labeling of the probe or antibody by coupling (e.g., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

In certain embodiments, detection of a nucleic acid of the invention in a biological sample involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Pat. Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) Science 241:1077-1080; and Nakazawa et al. (1994) PNAS 91:360-364), the latter of which can be particularly useful for distinguishing between orthologs of polynucleotides of the invention (see Abravaya et al. (1995) Nucleic Acids Res. 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a nucleic acid of the invention under conditions such that hybridization and amplification of the polynucleotide (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample.

In one aspect, the present invention contemplates a method for detecting the presence of *P. aeruginosa* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *P. aeruginosa*; (b) contacting the sample with an antibody reactive against eight consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4 under conditions which permit association between the antibody and its ligand; and

(c) detecting interaction of the antibody with its ligand, thereby detecting the presence of *P. aeruginosa* in the sample.

In another aspect, the present invention contemplates a method for detecting the presence of *P. aeruginosa* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *P. aeruginosa*; (b) contacting the sample with an antibody that binds specifically to a polypeptide of the invention under conditions which permit association between the antibody and its ligand; and (c) detecting interaction of the antibody with its ligand, thereby detecting the presence of *P. aeruginosa* in the sample.

In yet another example, the present invention contemplates a method for diagnosing a patient suffering from a *P. aeruginosa* related disease or disorder, comprising: (a) obtaining a biological sample from a patient; (b) detecting the presence or absence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the sample; and (c) diagnosing a patient suffering from a *P. aeruginosa* related disease or disorder based on the presence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the patient sample.

The diagnostic assays of the invention may also be used to monitor the effectiveness of an anti-*P. aeruginosa* treatment in an individual suffering from an *P. aeruginosa* related disease or disorder. For example, the presence and/or amount of a nucleic acid of the invention or a polypeptide of the invention can be detected in an individual suffering from an *P. aeruginosa* related disease or disorder before and after treatment with anti-*P. aeruginosa* therapeutic agent. Any change in the level of a polynucleotide or polypeptide of the invention after treatment of the individual with the therapeutic agent can provide information about the effectiveness of the treatment course. In particular, no change, or a decrease, in the level of a polynucleotide or polypeptide of the invention present in the biological sample will indicate that the therapeutic is successfully combating the *P. aeruginosa* related disease or disorder.

The invention also encompasses kits for detecting the presence of *P. aeruginosa* in a biological sample. For example, the kit can comprise a labeled or labelable compound or agent capable of detecting a polynucleotide or polypeptide of the invention in a biological sample; means for determining the amount of *P. aeruginosa* in the sample; and means for comparing the amount of *P. aeruginosa* in the sample with a standard. The compound or

agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect a polynucleotide or polypeptide of the invention.

9. Drug Discovery

Modulators to polypeptides of the invention and other structurally related molecules, and complexes containing the same, may be identified and developed as set forth below and otherwise using techniques and methods known to those of skill in the art. The modulators of the invention may be employed, for instance, to inhibit and treat *P. aeruginosa* associated diseases or conditions, such as osteomyelitis, otitis externa, conjunctivitis, keratitis, endophthalmitis, alveolar necrosis, vascular invasion, bacteremia, and burn infection.

A variety of methods for inhibiting the growth or infectivity of *P. aeruginosa* are contemplated by the present invention. For example, exemplary methods involve contacting *P. aeruginosa* with a polypeptide of the invention that modulates the same or another polypeptide from such pathogen, a nucleic acid encoding such polypeptide of the invention, or a compound thought or shown to be effective against such pathogen.

For example, in one aspect, the present invention contemplates a method for treating a patient suffering from an infection of *P. aeruginosa*, comprising administering to the patient an amount of a SEQ ID NO: 2 or SEQ ID NO: 4 inhibitor effective to inhibit the expression and/or activity of a polypeptide of the invention. In certain instances, the animal is a human or a livestock animal such as a cow, pig, goat or sheep. The present invention further contemplates a method for treating a subject suffering from a *P. aeruginosa* related disease or disorder, comprising administering to an animal having the condition a therapeutically effective amount of a molecule identified using one of the methods of the present invention.

The present invention contemplates making any molecule that is shown to modulate the activity of a polypeptide of the invention.

In another embodiment, inhibitors, modulators of the subject polypeptides, or biological complexes containing them, may be used in the manufacture of a medicament for any number of uses, including, for example, treating any disease or other treatable condition of a patient (including humans and animals), and particularly a disease caused by *P.*

aeruginosa, such as, for example, one of the following: osteomyelitis, otitis externa, conjunctivitis, keratitis, endophthalmitis, alveolar necrosis, vascular invasion, bacteremia, and burn infection..

(a) Drug Design

A number of techniques can be used to screen, identify, select and design chemical entities capable of associating with polypeptides of the invention, structurally homologous molecules, and other molecules. Knowledge of the structure for a polypeptide of the invention, determined in accordance with the methods described herein, permits the design and/or identification of molecules and/or other modulators which have a shape complementary to the conformation of a polypeptide of the invention, or more particularly, a druggable region thereof. It is understood that such techniques and methods may use, in addition to the exact structural coordinates and other information for a polypeptide of the invention, structural equivalents thereof described above (including, for example, those structural coordinates that are derived from the structural coordinates of amino acids contained in a druggable region as described above).

The term "chemical entity," as used herein, refers to chemical compounds, complexes of two or more chemical compounds, and fragments of such compounds or complexes. In certain instances, it is desirable to use chemical entities exhibiting a wide range of structural and functional diversity, such as compounds exhibiting different shapes (e.g., flat aromatic rings(s), puckered aliphatic rings(s), straight and branched chain aliphatics with single, double, or triple bonds) and diverse functional groups (e.g., carboxylic acids, esters, ethers, amines, aldehydes, ketones, and various heterocyclic rings).

In one aspect, the method of drug design generally includes computationally evaluating the potential of a selected chemical entity to associate with any of the molecules or complexes of the present invention (or portions thereof). For example, this method may include the steps of (a) employing computational means to perform a fitting operation between the selected chemical entity and a druggable region of the molecule or complex; and (b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the druggable region.

A chemical entity may be examined either through visual inspection or through the use of computer modeling using a docking program such as GRAM, DOCK, or AUTODOCK (Dunbrack et al., Folding & Design, 2:27-42 (1997)). This procedure can

include computer fitting of chemical entities to a target to ascertain how well the shape and the chemical structure of each chemical entity will complement or interfere with the structure of the subject polypeptide (Bugg et al., Scientific American, Dec.: 92-98 (1993); West et al., TIPS, 16:67-74 (1995)). Computer programs may also be employed to estimate the attraction, repulsion, and steric hindrance of the chemical entity to a druggable region, for example. Generally, the tighter the fit (e.g., the lower the steric hindrance, and/or the greater the attractive force) the more potent the chemical entity will be because these properties are consistent with a tighter binding constant. Furthermore, the more specificity in the design of a chemical entity the more likely that the chemical entity will not interfere with related proteins, which may minimize potential side-effects due to unwanted interactions.

A variety of computational methods for molecular design, in which the steric and electronic properties of druggable regions are used to guide the design of chemical entities, are known: Cohen et al. (1990) *J. Med. Cam.* 33: 883-894; Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288; DesJarlais (1988) *J. Med. Cam.* 31: 722-729; Bartlett et al. (1989) *Spec. Publ., Roy. Soc. Chem.* 78: 182-196; Goodford et al. (1985) *J. Med. Cam.* 28: 849-857; and DesJarlais et al. *J. Med. Cam.* 29: 2149-2153. Directed methods generally fall into two categories: (1) design by analogy in which 3-D structures of known chemical entities (such as from a crystallographic database) are docked to the druggable region and scored for goodness-of-fit; and (2) *de novo* design, in which the chemical entity is constructed piece-wise in the druggable region. The chemical entity may be screened as part of a library or a database of molecules. Databases which may be used include ACD (Molecular Designs Limited), NCI (National Cancer Institute), CCDC (Cambridge Crystallographic Data Center), CAST (Chemical Abstract Service), Derwent (Derwent Information Limited), Maybridge (Maybridge Chemical Company Ltd), Aldrich (Aldrich Chemical Company), DOCK (University of California in San Francisco), and the Directory of Natural Products (Chapman & Hall). Computer programs such as CONCORD (Tripos Associates) or DB-Converter (Molecular Simulations Limited) can be used to convert a data set represented in two dimensions to one represented in three dimensions.

Chemical entities may be tested for their capacity to fit spatially with a druggable region or other portion of a target protein. As used herein, the term "fits spatially" means that the three-dimensional structure of the chemical entity is accommodated geometrically by a druggable region. A favorable geometric fit occurs when the surface area of the

chemical entity is in close proximity with the surface area of the druggable region without forming unfavorable interactions. A favorable complementary interaction occurs where the chemical entity interacts by hydrophobic, aromatic, ionic, dipolar, or hydrogen donating and accepting forces. Unfavorable interactions may be steric hindrance between atoms in the chemical entity and atoms in the druggable region.

If a model of the present invention is a computer model, the chemical entities may be positioned in a druggable region through computational docking. If, on the other hand, the model of the present invention is a structural model, the chemical entities may be positioned in the druggable region by, for example, manual docking. As used herein the term "docking" refers to a process of placing a chemical entity in close proximity with a druggable region, or a process of finding low energy conformations of a chemical entity/druggable region complex.

In an illustrative embodiment, the design of potential modulator begins from the general perspective of shape complimentary for the druggable region of a polypeptide of the invention, and a search algorithm is employed which is capable of scanning a database of small molecules of known three-dimensional structure for chemical entities which fit geometrically with the target druggable region. Most algorithms of this type provide a method for finding a wide assortment of chemical entities that are complementary to the shape of a druggable region of the subject polypeptide. Each of a set of chemical entities from a particular data-base, such as the Cambridge Crystallographic Data Bank (CCDB) (Allen et al. (1973) *J. Chem. Doc.* 13: 119), is individually docked to the druggable region of a polypeptide of the invention in a number of geometrically permissible orientations with use of a docking algorithm. In certain embodiments, a set of computer algorithms called DOCK, can be used to characterize the shape of invaginations and grooves that form the active sites and recognition surfaces of the druggable region (Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288). The program can also search a database of small molecules for templates whose shapes are complementary to particular binding sites of a polypeptide of the invention (DesJarlais et al. (1988) *J Med Chem* 31: 722-729).

The orientations are evaluated for goodness-of-fit and the best are kept for further examination using molecular mechanics programs, such as AMBER or CHARMM. Such algorithms have previously proven successful in finding a variety of chemical entities that are complementary in shape to a druggable region.

Goodford (1985, *J Med Chem* 28:849-857) and Boobbyer et al. (1989, *J Med Chem* 32:1083-1094) have produced a computer program (GRID) which seeks to determine regions of high affinity for different chemical groups (termed probes) of the druggable region. GRID hence provides a tool for suggesting modifications to known chemical entities that might enhance binding. It may be anticipated that some of the sites discerned by GRID as regions of high affinity correspond to "pharmacophoric patterns" determined inferentially from a series of known ligands. As used herein, a "pharmacophoric pattern" is a geometric arrangement of features of chemical entities that is believed to be important for binding. Attempts have been made to use pharmacophoric patterns as a search screen for novel ligands (Jakes et al. (1987) *J Mol Graph* 5:41-48; Brint et al. (1987) *J Mol Graph* 5:49-56; Jakes et al. (1986) *J Mol Graph* 4:12-20).

Yet a further embodiment of the present invention utilizes a computer algorithm such as CLIX which searches such databases as CCDB for chemical entities which can be oriented with the druggable region in a way that is both sterically acceptable and has a high likelihood of achieving favorable chemical interactions between the chemical entity and the surrounding amino acid residues. The method is based on characterizing the region in terms of an ensemble of favorable binding positions for different chemical groups and then searching for orientations of the chemical entities that cause maximum spatial coincidence of individual candidate chemical groups with members of the ensemble. The algorithmic details of CLIX is described in Lawrence et al. (1992) *Proteins* 12:31-41.

In this way, the efficiency with which a chemical entity may bind to or interfere with a druggable region may be tested and optimized by computational evaluation. For example, for a favorable association with a druggable region, a chemical entity must preferably demonstrate a relatively small difference in energy between its bound and fine states (i.e., a small deformation energy of binding). Thus, certain, more desirable chemical entities will be designed with a deformation energy of binding of not greater than about 10 kcal/mole, and more preferably, not greater than 7 kcal/mole. Chemical entities may interact with a druggable region in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free entity and the average energy of the conformations observed when the chemical entity binds to the target.

In this way, the present invention provides computer-assisted methods for identifying or designing a potential modulator of the activity of a polypeptide of the

invention including: supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region from a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the activity of a polypeptide of the invention.

In another aspect, the present invention provides a computer-assisted method for identifying or designing a potential modulator to a polypeptide of the invention, supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region of a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates for a chemical entity; evaluating the potential binding interactions between the chemical entity and active site of the molecule or molecular complex; structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, and determining whether the modified chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the polypeptide of the invention.

In one embodiment, a potential modulator can be obtained by screening a peptide library (Scott and Smith, Science, 249:386-390 (1990); Cwirla et al., Proc. Natl. Acad. Sci., 87:6378-6382 (1990); Devlin et al., Science, 249:404-406 (1990)). A potential modulator selected in this manner could then be systematically modified by computer modeling programs until one or more promising potential drugs are identified. Such analysis has been shown to be effective in the development of HIV protease inhibitors (Lam et al., Science 263:380-384 (1994); Wlodawer et al., Ann. Rev. Biochem. 62:543-585 (1993); Appelt, Perspectives in Drug Discovery and Design 1:23-48 (1993); Erickson, Perspectives in Drug Discovery and Design 1:109-128 (1993)). Alternatively a potential modulator may be selected from a library of chemicals such as those that can be licensed from third parties, such as chemical and pharmaceutical companies. A third alternative is to synthesize the potential modulator *de novo*.

For example, in certain embodiments, the present invention provides a method for making a potential modulator for a polypeptide of the invention, the method including synthesizing a chemical entity or a molecule containing the chemical entity to yield a

potential modulator of a polypeptide of the invention, the chemical entity having been identified during a computer-assisted process including supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least one druggable region from a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to the molecule or complex at the active site, wherein binding to the molecule or complex is indicative of potential modulation. This method may further include the steps of evaluating the potential binding interactions between the chemical entity and the active site of the molecule or molecular complex and structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, which steps may be repeated one or more times.

Once a potential modulator is identified, it can then be tested in any standard assay for the macromolecule depending of course on the macromolecule, including in high throughput assays. Further refinements to the structure of the modulator will generally be necessary and can be made by the successive iterations of any and/or all of the steps provided by the particular screening assay, in particular further structural analysis by e.g., ^{15}N NMR relaxation rate determinations or x-ray crystallography with the modulator bound to the subject polypeptide. These studies may be performed in conjunction with biochemical assays.

Once identified, a potential modulator may be used as a model structure, and analogs to the compound can be obtained. The analogs are then screened for their ability to bind the subject polypeptide. An analog of the potential modulator might be chosen as a modulator when it binds to the subject polypeptide with a higher binding affinity than the predecessor modulator.

In a related approach, iterative drug design is used to identify modulators of a target protein. Iterative drug design is a method for optimizing associations between a protein and a modulator by determining and evaluating the three dimensional structures of successive sets of protein/modulator complexes. In iterative drug design, crystals of a series of protein/modulator complexes are obtained and then the three-dimensional structures of each complex is solved. Such an approach provides insight into the association between the proteins and modulators of each complex. For example, this approach may be accomplished by selecting modulators with inhibitory activity, obtaining crystals of this

new protein/modulator complex, solving the three dimensional structure of the complex, and comparing the associations between the new protein/modulator complex and previously solved protein/modulator complexes. By observing how changes in the modulator affected the protein/modulator associations, these associations may be optimized.

In addition to designing and/or identifying a chemical entity to associate with a druggable region, as described above, the same techniques and methods may be used to design and/or identify chemical entities that either associate, or do not associate, with affinity regions, selectivity regions or undesired regions of protein targets. By such methods, selectivity for one or a few targets, or alternatively for multiple targets, from the same species or from multiple species, can be achieved.

For example, a chemical entity may be designed and/or identified for which the binding energy for one druggable region, e.g., an affinity region or selectivity region, is more favorable than that for another region, e.g., an undesired region, by about 20%, 30%, 50% to about 60% or more. It may be the case that the difference is observed between (a) more than two regions, (b) between different regions (selectivity, affinity or undesirable) from the same target, (c) between regions of different targets, (d) between regions of homologs from different species, or (e) between other combinations. Alternatively, the comparison may be made by reference to the K_d, usually the apparent K_d, of said chemical entity with the two or more regions in question.

In another aspect, prospective modulators are screened for binding to two nearby druggable regions on a target protein. For example, a modulator that binds a first region of a target polypeptide does not bind a second nearby region. Binding to the second region can be determined by monitoring changes in a different set of amide chemical shifts in either the original screen or a second screen conducted in the presence of a modulator (or potential modulator) for the first region. From an analysis of the chemical shift changes, the approximate location of a potential modulator for the second region is identified. Optimization of the second modulator for binding to the region is then carried out by screening structurally related compounds (e.g., analogs as described above). When modulators for the first region and the second region are identified, their location and orientation in the ternary complex can be determined experimentally. On the basis of this structural information, a linked compound, e.g., a consolidated modulator, is synthesized in which the modulator for the first region and the modulator for the second region are linked. In certain embodiments, the two modulators are covalently linked to form a consolidated

modulator. This consolidated modulator may be tested to determine if it has a higher binding affinity for the target than either of the two individual modulators. A consolidated modulator is selected as a modulator when it has a higher binding affinity for the target than either of the two modulators. Larger consolidated modulators can be constructed in an analogous manner, e.g., linking three modulators which bind to three nearby regions on the target to form a multilinked consolidated modulator that has an even higher affinity for the target than the linked modulator. In this example, it is assumed that is desirable to have the modulator bind to all the druggable regions. However, it may be the case that binding to certain of the druggable regions is not desirable, so that the same techniques may be used to identify modulators and consolidated modulators that show increased specificity based on binding to at least one but not all druggable regions of a target.

The present invention provides a number of methods that use drug design as described above. For example, in one aspect, the present invention contemplates a method for designing a candidate compound for screening for inhibitors of a polypeptide of the invention, the method comprising: (a) determining the three dimensional structure of a crystallized polypeptide of the invention or a fragment thereof; and (b) designing a candidate inhibitor based on the three dimensional structure of the crystallized polypeptide or fragment.

In another aspect, the present invention contemplates a method for identifying a potential inhibitor of a polypeptide of the invention, the method comprising: (a) providing the three-dimensional coordinates of a polypeptide of the invention or a fragment thereof; (b) identifying a druggable region of the polypeptide or fragment; and (c) selecting from a database at least one compound that comprises three dimensional coordinates which indicate that the compound may bind the druggable region; (d) wherein the selected compound is a potential inhibitor of a polypeptide of the invention.

In another aspect, the present invention contemplates a method for identifying a potential modulator of a molecule comprising a druggable region similar to that of SEQ ID NO: 2 or SEQ ID NO: 4, the method comprising: (a) using the atomic coordinates of amino acid residues from SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a druggable region that is a portion of SEQ ID NO: 2 or SEQ ID NO: 4; (b) employing the three dimensional structure to design or select the potential modulator; (c) synthesizing the modulator; and

(d) contacting the modulator with the molecule to determine the ability of the modulator to interact with the molecule.

In another aspect, the present invention contemplates an apparatus for determining whether a compound is a potential inhibitor of a polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, the apparatus comprising: (a) a memory that comprises: (i) the three dimensional coordinates and identities of the atoms of a polypeptide of the invention or a fragment thereof that form a druggable site; and (ii) executable instructions; and (b) a processor that is capable of executing instructions to: (i) receive three-dimensional structural information for a candidate compound; (ii) determine if the three-dimensional structure of the candidate compound is complementary to the structure of the interior of the druggable site; and (iii) output the results of the determination.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *P. aeruginosa* related disease or disorder, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *P. aeruginosa* related disease or disorder based on the three dimensional structure of the crystallized polypeptide or fragment; (c) contacting a polypeptide of the present invention or an *P. aeruginosa* with the potential compound; and (d) assaying the activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *P. aeruginosa* related disease or disorder.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *P. aeruginosa* related disease or disorder, the method comprising: (a) providing structural information of a druggable region derived from NMR spectroscopy of a polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *P. aeruginosa* related disease or disorder based on the structural information; (c) contacting a polypeptide of the present invention or an *P. aeruginosa* with the potential compound; and (d) assaying the activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *P. aeruginosa* related disease or disorder.

(b) In Vitro Assays

Polypeptides of the invention may be used to assess the activity of small molecules and other modulators in *in vitro* assays. In one embodiment of such an assay, agents are identified which modulate the biological activity of a protein, protein-protein interaction of interest or protein complex, such as an enzymatic activity, binding to other cellular components, cellular compartmentalization, signal transduction, and the like. In certain embodiments, the test agent is a small organic molecule.

Assays may employ kinetic or thermodynamic methodology using a wide variety of techniques including, but not limited to, microcalorimetry, circular dichroism, capillary zone electrophoresis, nuclear magnetic resonance spectroscopy, fluorescence spectroscopy, and combinations thereof.

The invention also provides a method of screening compounds to identify those which modulate the action of polypeptides of the invention, or polynucleotides encoding the same. The method of screening may involve high-throughput techniques. For example, to screen for modulators, a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, comprising a polypeptide of the invention and a labeled substrate or ligand of such polypeptide is incubated in the absence or the presence of a candidate molecule that may be a modulator of a polypeptide of the invention. The ability of the candidate molecule to modulate a polypeptide of the invention is reflected in decreased binding of the labeled ligand or decreased production of product from such substrate. Detection of the rate or level of production of product from substrate may be enhanced by using a reporter system. Reporter systems that may be useful in this regard include but are not limited to colorimetric labeled substrate converted into product, a reporter gene that is responsive to changes in a nucleic acid of the invention or polypeptide activity, and binding assays known in the art.

Another example of an assay for a modulator of a polypeptide of the invention is a competitive assay that combines a polypeptide of the invention and a potential modulator with molecules that bind to a polypeptide of the invention, recombinant molecules that bind to a polypeptide of the invention, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. Polypeptides of the invention can be labeled, such as by radioactivity or a colorimetric compound, such that

the number of molecules of a polypeptide of the invention bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the potential modulator.

A number of methods for identifying a molecule which modulates the activity of a polypeptide are known in the art. For example, in one such method, a subject polypeptide is contacted with a test compound, and the activity of the subject polypeptide in the presence of the test compound is determined, wherein a change in the activity of the subject polypeptide is indicative that the test compound modulates the activity of the subject polypeptide. In certain instances, the test compound agonizes the activity of the subject polypeptide, and in other instances, the test compound antagonizes the activity of the subject polypeptide.

In another example, a compound which modulates SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *P. aeruginosa* may be identified by (a) contacting a polypeptide of the invention with a test compound; and (b) determining the activity of the polypeptide in the presence of the test compound, wherein a change in the activity of the polypeptide is indicative that the test compound may modulate the growth or infectivity of *P. aeruginosa*.

(c) In Vivo Assays

Animal models of bacterial infection and/or disease may be used as an *in vivo* assay for evaluating the effectiveness of a potential drug target in treating or preventing *P. aeruginosa* related diseases or disorders. A number of suitable animal models are described briefly below, however, these models are only examples and modifications, or completely different animal models, may be used in accord with the methods of the invention.

(i) Mouse Soft Tissue Model

The mouse soft tissue infection model is a sensitive and effective method for measurement of bacterial proliferation. In these models (Vogelman et al., 1988, J. Infect. Dis. 157: 287-298) anesthetized mice are infected with the bacteria in the muscle of the hind thigh. The mice can be either chemically immune compromised (e.g., cytoxan treated at 125 mg/kg on days -4, -2, and 0) or immunocompetent. The dose of microbe necessary to cause an infection is variable and depends on the individual microbe, but commonly is on the order of 10^5 - 10^6 colony forming units per injection for bacteria. A variety of mouse strains are useful in this model although Swiss Webster and DBA2 lines are most

commonly used. Once infected the animals are conscious and show no overt ill effects of the infections for approximately 12 hours. After that time virulent strains cause swelling of the thigh muscle, and the animals can become bacteremic within approximately 24 hours. This model most effectively measures proliferation of the microbe, and this proliferation is measured by sacrifice of the infected animal and counting colonies from homogenized thighs.

(ii) Diffusion Chamber Model

A second model useful for assessing the virulence of microbes is the diffusion chamber model (Malouin et al., 1990, Infect. Immun. 58: 1247-1253; Doy et al., 1980, J. Infect. Dis. 2: 39-51; Kelly et al., 1989, Infect. Immun. 57: 344-350. In this model rodents have a diffusion chamber surgically placed in the peritoneal cavity. The chamber consists of a polypropylene cylinder with semipermeable membranes covering the chamber ends. Diffusion of peritoneal fluid into and out of the chamber provides nutrients for the microbes. The progression of the "infection" may be followed by examining growth, the exoproduct production or RNA messages. The time experiments are done by sampling multiple chambers.

(iii) Endocarditis Model

For bacteria, an important animal model effective in assessing pathogenicity and virulence is the endocarditis model (J. Santoro and M. E. Levinson, 1978, Infect. Immun. 19: 915-918). A rat endocarditis model can be used to assess colonization, virulence and proliferation.

(iv) Osteomyelitis Model

A fourth model useful in the evaluation of pathogenesis is the osteomyelitis model (Spagnolo et al., 1993, Infect. Immun. 61: 5225-5230). Rabbits are used for these experiments. Anesthetized animals have a small segment of the tibia removed and microorganisms are microinjected into the wound. The excised bone segment is replaced and the progression of the disease is monitored. Clinical signs, particularly inflammation and swelling are monitored. Termination of the experiment allows histolic and pathologic examination of the infection site to complement the assessment procedure.

(v) Murine Septic Arthritis Model

A fifth model relevant to the study of microbial pathogenesis is a murine septic arthritis model (Abdelnour et al., 1993, Infect. Immun. 61: 3879-3885). In this model mice are infected intravenously and pathogenic organisms are found to cause inflammation in distal limb joints. Monitoring of the inflammation and comparison of inflammation vs. inocula allows assessment of the virulence of related strains.

(vi) Bacterial Peritonitis Model

Finally, bacterial peritonitis offers rapid and predictive data on the virulence of strains (M. G. Bergeron, 1978, Scand. J. Infect. Dis. Suppl. 14: 189-206; S. D. Davis, 1975, Antimicrob. Agents Chemother. 8: 50-53). Peritonitis in rodents, such as mice, can provide essential data on the importance of targets. The end point may be lethality or clinical signs can be monitored. Variation in infection dose in comparison to outcome allows evaluation of the virulence of individual strains.

A variety of other *in vivo* models are available and may be used when appropriate for specific pathogens or specific test agents. For example, target organ recovery assays (Gordee et al., 1984, J. Antibiotics 37:1054-1065; Bannatyne et al., 1992, Infect. 20:168-170) may be useful for fungi and for bacterial pathogens which are not acutely virulent to animals.

It is also relevant to note that the species of animal used for an infection model, and the specific genetic make-up of that animal, may contribute to the effective evaluation of the effects of a particular test agent. For example, immuno-incompetent animals may, in some instances, be preferable to immuno-competent animals. For example, the action of a competent immune system may, to some degree, mask the effects of the test agent as compared to a similar infection in an immuno-incompetent animal. In addition, many opportunistic infections, in fact, occur in immuno-compromised patients, so modeling an infection in a similar immunological environment is appropriate.

10. Vaccines

There are provided by the invention, products, compositions and methods for raising immunological response against a pathogen, especially *P. aeruginosa*. In one aspect, a polypeptide of the invention or a nucleic acid of the invention, or an antigenic fragment

thereof, may be administered to a subject, optionally with a booster, adjuvant, or other composition that stimulates immune responses.

Another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal which comprises inoculating the individual with a polypeptide of the invention and/or a nucleic acid of the invention, adequate to produce antibody and/or T cell immune response to protect said individual from infection, particularly bacterial infection and most particularly *P. aeruginosa* infection. Also provided are methods whereby such immunological response slows bacterial replication. Yet another aspect of the invention relates to a method of inducing immunological response in an individual which comprises delivering to such individual a nucleic acid vector, sequence or ribozyme to direct expression of a polypeptide of the invention and/or a nucleic acid of the invention *in vivo* in order to induce an immunological response, such as, to produce antibody and/or T cell immune response, including, for example, cytokine-producing T cells or cytotoxic T cells, to protect said individual, preferably a human, from disease, whether that disease is already established within the individual or not. One example of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a ribozyme, a modified nucleic acid, a DNA/RNA hybrid, a DNA-protein complex or an RNA-protein complex.

A further aspect of the invention relates to an immunological composition that when introduced into an individual, preferably a human, capable of having induced within it an immunological response, induces an immunological response in such individual to a nucleic acid of the invention and/or a polypeptide encoded therefrom, wherein the composition comprises a recombinant nucleic acid of the invention and/or polypeptide encoded therefrom and/or comprises DNA and/or RNA which encodes and expresses an antigen of said nucleic acid of the invention, polypeptide encoded therefrom, or other polypeptide of the invention. The immunological response may be used therapeutically or prophylactically and may take the form of antibody immunity and/or cellular immunity, such as cellular immunity arising from CTL or CD4+T cells.

In another embodiment, the invention relates to compositions comprising a polypeptide of the invention and an adjuvant. The adjuvant can be any vehicle which would typically enhance the antigenicity of a polypeptide, e.g., minerals (for instance, alum, aluminum hydroxide or aluminum phosphate), saponins complexed to membrane protein

antigens (immune stimulating complexes), pluronic polymers with mineral oil, killed mycobacteria in mineral oil, Freund's complete adjuvant, bacterial products, such as muramyl dipeptide (MDP) and lipopolysaccharide (LPS), as well as lipid A, liposomes, or any of the other adjuvants known in the art. A polypeptide of the invention can be emulsified with, absorbed onto, or coupled with the adjuvant.

A polypeptide of the invention may be fused with co-protein or chemical moiety which may or may not by itself produce antibodies, but which is capable of stabilizing the first protein and producing a fused or modified protein which will have antigenic and/or immunogenic properties, and preferably protective properties. Thus fused recombinant protein, may further comprise an antigenic co-protein, such as lipoprotein D from Hemophilus influenzae, Glutathione-S-transferase (GST) or beta-galactosidase, or any other relatively large co-protein which solubilizes the protein and facilitates production and purification thereof. Moreover, the co-protein may act as an adjuvant in the sense of providing a generalized stimulation of the immune system of the organism receiving the protein. The co-protein may be attached to either the amino- or carboxy-terminus of a polypeptide of the invention.

Provided by this invention are compositions, particularly vaccine compositions, and methods comprising the polypeptides and/or polynucleotides of the invention and immunostimulatory DNA sequences, such as those described in Sato, Y. et al. Science 273: 352 (1996).

Also, provided by this invention are methods using the described polynucleotide or particular fragments thereof, which have been shown to encode non-variable regions of bacterial cell surface proteins, in polynucleotide constructs used in such genetic immunization experiments in animal models of infection with *P. aeruginosa*. Such experiments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. It is believed that this approach will allow for the subsequent preparation of monoclonal antibodies of particular value, derived from the requisite organ of the animal successfully resisting or clearing infection, for the development of prophylactic agents or therapeutic treatments of bacterial infection, particularly *P. aeruginosa* infection, in mammals, particularly humans.

A polypeptide of the invention may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by blocking adherence of bacteria to damaged tissue.

11. Array Analysis

In part, the present invention is directed to the use of subject nucleic acids in arrays to assess gene expression. In another part, the present invention is directed to the use of subject nucleic acids in arrays for *P. aeruginosa*. In yet another part, the present invention contemplates using the subject nucleic acids to interact with probes contained on arrays.

In one aspect, the present invention contemplates an array comprising a substrate having a plurality of addresses, wherein at least one of the addresses has disposed thereon a capture probe that can specifically bind to a nucleic acid of the invention. In another aspect, the present invention contemplates a method for detecting expression of a nucleotide sequence which encodes a polypeptide of the invention, or a fragment thereof, using the foregoing array by: (a) providing a sample comprising at least one mRNA molecule; (b) exposing the sample to the array under conditions which promote hybridization between the capture probe disposed on the array and a nucleic acid complementary thereto; and (c) detecting hybridization between an mRNA molecule of the sample and the capture probe disposed on the array, thereby detecting expression of a sequence which encodes for a polypeptide of the invention, or a fragment thereof.

Arrays are often divided into microarrays and macroarrays, where microarrays have a much higher density of individual probe species per area. Microarrays may have as many as 1000 or more different probes in a 1 cm^2 area. There is no concrete cut-off to demarcate the difference between micro- and macroarrays, and both types of arrays are contemplated for use with the invention.

Microarrays are known in the art and generally consist of a surface to which probes that correspond in sequence to gene products (e.g., cDNAs, mRNAs, oligonucleotides) are bound at known positions. In one embodiment, the microarray is an array (e.g., a matrix) in which each position represents a discrete binding site for a product encoded by a gene (e.g., a protein or RNA), and in which binding sites are present for products of most or almost all of the genes in the organism's genome. In certain embodiments, the binding site or site is a nucleic acid or nucleic acid analogue to which a particular cognate cDNA can specifically

hybridize. The nucleic acid or analogue of the binding site may be, e.g., a synthetic oligomer, a full-length cDNA, a less-than full length cDNA, or a gene fragment.

Although in certain embodiments the microarray contains binding sites for products of all or almost all genes in the target organism's genome, such comprehensiveness is not necessarily required. Usually the microarray will have binding sites corresponding to at least 100, 500, 1000, 4000 genes or more. In certain embodiments, arrays will have anywhere from about 50, 60, 70 , 80, 90, or even more than 95% of the genes of a particular organism represented. The microarray typically has binding sites for genes relevant to testing and confirming a biological network model of interest. Several exemplary human microarrays are publicly available.

The probes to be affixed to the arrays are typically polynucleotides. These DNAs can be obtained by, e.g., polymerase chain reaction (PCR) amplification of gene segments from genomic DNA, cDNA (e.g., by RT-PCR), or cloned sequences. PCR primers are chosen, based on the known sequence of the genes or cDNA, that result in amplification of unique fragments (e.g., fragments that do not share more than 10 bases of contiguous identical sequence with any other fragment on the microarray). Computer programs are useful in the design of primers with the required specificity and optimal amplification properties. See, e.g., Oligo pl version 5.0 (National Biosciences). In an alternative embodiment, the binding (hybridization) sites are made from plasmid or phage clones of genes, cDNAs (e.g., expressed sequence tags), or inserts therefrom (Nguyen et al., 1995, Genomics 29:207-209).

A number of methods are known in the art for affixing the nucleic acids or analogues to a solid support that makes up the array (Schena et al., 1995, Science 270:467-470; DeRisi et al., 1996, Nature Genetics 14:457-460; Shalon et al., 1996, Genome Res. 6:639-645; and Schena et al., 1995, Proc. Natl. Acad. Sci. USA 93:10539-11286).

Another method for making microarrays is by making high-density oligonucleotide arrays (Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. USA 91:5022-5026; Lockhart et al., 1996, Nature Biotech 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270; Blanchard et al., 1996, 11: 687-90).

Other methods for making microarrays, e.g., by masking (Maskos and Southern, 1992, Nuc. Acids Res. 20:1679-1684), may also be used. In principal, any type of array, for example, dot blots on a nylon hybridization membrane (see Sambrook et al., Molecular

Cloning - A Laboratory Manual (2nd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989), could be used, although, as will be recognized by those of skill in the art.

The nucleic acids to be contacted with the microarray may be prepared in a variety of ways, and may include nucleotides of the subject invention. Such nucleic acids are often labeled fluorescently. Nucleic acid hybridization and wash conditions are chosen so that the population of labeled nucleic acids will specifically hybridize to appropriate, complementary nucleic acids affixed to the matrix. Non-specific binding of the labeled nucleic acids to the array can be decreased by treating the array with a large quantity of non-specific DNA – a so-called "blocking" step.

When fluorescently labeled probes are used, the fluorescence emissions at each site of a transcript array may be detected by scanning confocal laser microscopy. When two fluorophores are used, a separate scan, using the appropriate excitation line, is carried out for each of the two fluorophores used. Fluorescent microarray scanners are commercially available from Affymetrix, Packard BioChip Technologies, BioRobotics and many other suppliers. Signals are recorded, quantitated and analyzed using a variety of computer software.

According to the method of the invention, the relative abundance of an mRNA in two cells or cell lines is scored as a perturbation and its magnitude determined (i.e., the abundance is different in the two sources of mRNA tested), or as not perturbed (i.e., the relative abundance is the same). As used herein, a difference between the two sources of RNA of at least a factor of about 25% (RNA from one source is 25% more abundant in one source than the other source), more usually about 50%, even more often by a factor of about 2 (twice as abundant), 3 (three times as abundant) or 5 (five times as abundant) is scored as a perturbation. Present detection methods allow reliable detection of difference of an order of about 2-fold to about 5-fold, but more sensitive methods are expected to be developed.

In addition to identifying a perturbation as positive or negative, it is advantageous to determine the magnitude of the perturbation. This can be carried out, as noted above, by calculating the ratio of the emission of the two fluorophores used for differential labeling, or by analogous methods that will be readily apparent to those of skill in the art.

In certain embodiments, the data obtained from such experiments reflects the relative expression of each gene represented in the microarray.. Expression levels in

different samples and conditions may now be compared using a variety of statistical methods.

12. Pharmaceutical Compositions

Pharmaceutical compositions of this invention include any modulator identified according to the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The term "pharmaceutically acceptable carrier" refers to a carrier(s) that is "acceptable" in the sense of being compatible with the other ingredients of a composition and not deleterious to the recipient thereof.

Methods of making and using such pharmaceutical compositions are also included in the invention. The pharmaceutical compositions of the invention can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra articular, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the modulators described herein are useful for the prevention and treatment of disease and conditions, including *P. aeruginosa* mediated diseases and conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

13. Antimicrobial Agents

The polypeptides of the invention may be used to develop antimicrobial agents for use in a wide variety of applications. The uses are as varied as surface disinfectants, topical pharmaceuticals, personal hygiene applications (e.g., antimicrobial soap, deodorant or the like), additives to cell culture medium, and systemic pharmaceutical products. Antimicrobial agents of the invention may be incorporated into a wide variety of products

and used to treat an already existing microbial infection/contamination or may be used prophylactically to suppress future infection/contamination.

The antimicrobial agents of the invention may be administered to a site, or potential site, of infection/contamination in either a liquid or solid form. Alternatively, the agent may be applied as a coating to a surface of an object where microbial growth is undesirable using nonspecific absorption or covalent attachment. For example, implants or devices (such as linens, cloth, plastics, heart pacemakers, surgical stents, catheters, gastric tubes, endotracheal tubes, prosthetic devices) can be coated with the antimicrobials to minimize adherence or persistence of bacteria during storage and use. The antimicrobials may also be incorporated into such devices to provide slow release of the agent locally for several weeks during healing. The antimicrobial agents may also be used in association with devices such as ventilators, water reservoirs, air-conditioning units, filters, paints, or other substances. Antimicrobials of the invention may also be given orally or systemically after transplantation, bone replacement, during dental procedures, or during implantation to prevent colonization with bacteria.

In another embodiment, antimicrobial agents of the invention may be used as a food preservative or in treating food products to eliminate potential pathogens. The latter use might be targeted to the fish and poultry industries that have serious problems with enteric pathogens which cause severe human disease. In a further embodiment, the agents of the invention may be used as antimicrobials for food crops, either as agents to reduce post harvest spoilage or to enhance host resistance. The antimicrobials may also be used as preservatives in processed foods either alone or in combination with antibacterial food additives such as lysozymes.

In another embodiment, the antimicrobials of the invention may be used as an additive to culture medium to prevent or eliminate infection of cultured cells with a pathogen.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

EXAMPLE 1 Isolation and Cloning of Nucleic Acid

Pseudomonas aeruginosa is an opportunistic Gram-negative bacilli found in sewage, plants, and sometimes the intestine. It is capable of infecting various organs and has been identified in numerous infections including those in the ears, lungs, urinary tract, blood and in burns and surgical wound infections. Polynucleotide sequences were obtained from The Institute of Genomic Research (TIGR) (Rockville, MD; www.tigr.org). Chromosomal DNA was acquired from the American Type Culture Collection (ATCC; reference #17933D).

The coding sequence of the polynucleotide having SEQ ID NO: 1 is obtained by reference to either publicly available databases or from the use of a bioinformatics program that is used to select the coding sequence of interest from the genome. For example, coding sequences for the genome of *P. aeruginosa* may be obtained from NCBI (http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/framik?db=Genome&gi=163).

The coding DNA is amplified from purified genomic DNA using PCR with primers that are identified with a computer program. The PCR primers are selected so as to introduce restriction enzyme cleavage sites at the flanking regions of the DNA (e.g., Nde1 and BglII). The forward and reverse primers have SEQ ID NO: 5 and SEQ ID NO: 6. The sequences of the primers are shown in FIGURE 5, and their respective restriction sites and melting temperatures are shown in Table 1 of FIGURE 6.

The PCR reaction is performed using 50-100 *ng* of chromosomal DNA and 2 Units of a high fidelity DNA Polymerase (for example *Pfu* Turbo (Stratagene) or Platinum *Pfx* (Invitrogen)). The thermocycling conditions for the PCR process include a DNA melting step at 94°C for 45 sec, a primer annealing step at 48°C - 58°C (depending on Primer [Tm]) for 45 sec, and an extension step at 68°C – 72°C (depending on enzyme) for 1 min 45 sec – 2 min 30 sec (depending on size of DNA). After 25-30 cycles, a final blocking step at 72°C for 9 min is carried out.

The amplified nucleic acid product is isolated from the PCR cocktail using silica-gel membrane based column chromatography (Qiagen). The quality of the PCR product is assessed by resolving an aliquot of amplified product on a 1% agarose gel. The DNA is quantified spectrophotometrically at A_{260} or by visualizing the resolved genes with a 302 nm UV-B light source.

The PCR product is directionally cloned into the polylinker region of any of three expression vectors: pET28 (Novagen), pET15 (Novagen) or pGEX (Pharmacia/LKB Biotechnology). Additional restriction enzyme sites may be engineered into the expressions vectors to allow for simultaneous clones to be prepared having different purification tags. After the ligation reaction, the DNA is transformed into competent *E. coli* cells (Strains XL1-Blue (Stratagene) or DH5α (Invitrogen)) via heat shock or electroporation as described in Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). The expression vectors contain the bacteriophage T7 promoter for RNA polymerase, and the *E. coli* strain used produces T7 RNA polymerase upon induction with isopropyl-β-D-thiogalactoside (IPTG). The sequence of the cloning site adds a Glutathione S-transferase (GST) tag, or a polyhistidine (6X His) tag, at the N- or C– terminus of the recombinant protein. The cloning site also inserts a cleavage site for the thrombin or Tev (Invitrogen) enzymes between the recombinant protein and the N- or C- terminal GST or polyhistidine tag.

Transformants are selected using the appropriate antibiotic (Ampicillin or Kanamycin) and identified using PCR, or another method, to analyze their DNA. The polynucleotide sequence cloned into the expression construct is then isolated using a modified alkaline lysis method (Birnboim, H.C., and Doly, J. (1979) *Nucl. Acids Res.* 7, 1513-1522.) The sequence of the clone is verified by standard polynucleotide sequencing methods. The published nucleic acid and amino acid sequences are presented in FIGURE 1 and FIGURE 2. The experimentally determined nucleic acid sequence is presented in FIGURE 3, and the amino acid sequence predicted from the sequence of FIGURE 3 is presented in FIGURE 4.

The expression construct is transformed into a bacterial host strain BL21-Gold (DE3) supplemented with a plasmid called pUBS520, which directs expression of tRNA for arginine (agg and aga) and serves to augment the expression of the recombinant protein in the host cell (Gene, vol. 85 (1989) 109-114). The expression construct may also be transformed into BL21-Gold (DE3) without pUBS520, BL21-Gold (DE3) Codon-Plus (RIL) or (RP) (Stratagene) or Roseatta (DE3) (Novagen), the latter two of which contain genes encoding tRNAs. Alternatively, the expression construct may be transformed into BL21 STAR *E. coli* (Invitrogen) cells which has an Rnase deficiency that reduces degradation of recombinant mRNA transcript and therefore increases the protein yield. The

recombinant protein is then assayed for positive overexpression in the host and the presence of the protein in the cytoplasmic (water soluble) region of the cell.

EXAMPLE 2 Expressing Polypeptides of the Invention

(a) Test Expression

Transformed cells are grown in LB medium supplemented with the appropriate antibiotics up to a final concentration of 100 μg/ml. The cultures are shaken at 37°C until they reach an optical density (OD_{600}) between 0.6 and 0.7. The cultures are then induced with isopropyl-beta-D-thiogalactopyranoside (IPTG) to a final concentration of 0.5 mM at 15°C for 10 hours, 25°C for 4 hours, or 30°C for 4 hours.

(b) Method One for Determining Protein Solubility Levels

The cells are harvested by centrifugation and subjected to a freeze/thaw cycle. The cells are lysed using detergent, sonication, or incubation with lysozyme. Total and soluble proteins are assayed using a 26-well BioRad Criterion gel running system. The proteins are stained with an appropriate dye (Coomassie, Silver stain, or Sypro-Red) and visualized with the appropriate visualization system. Typically recombinant protein is seen as a prominent band in the lanes of the gel representing the soluble fraction.

(c) Method Two for Determining Protein Solubility Levels

The soluble and insoluble fractions (in the presence of 6M urea) of the cell pellet are bound to the appropriate affinity column. The purified proteins from both fractions are analysed by SDS-PAGE and the levels of protein in the soluble fraction are determined.

The approximate percent solubility of the polypeptide having the sequence of SEQ ID NO: 4 is determined using one of the foregoing methods, and the resulting percent solubility is presented in Table 1 of FIGURE 6.

(d) Native Protein Expression

The expression construct clone encoding the soluble polypeptide having the amino acid sequence of SEQ ID NO: 4 is introduced into an expression host. The resultant cell line is then grown in culture. The method of growth is dependant on whether the protein to be purified is a native protein or a labeled protein. For native and ^{15}N labeled protein production, a Gold-pUBS520 (as described above), BL21-Gold (DE3) Codon-Plus (RIL) or

(RP), or BL21 STAR *E. Coli* cell line is used. For generating proteins metabolically labeled with selenium, the clone is introduced into a strain called B834 (Novagen). The methods for expressing labeled polypeptides of the invention are described in the Examples that follow.

In one method for expressing an unlabeled polypeptide of the invention, 2L LB cultures or 1L TB cultures are inoculated with a 1% (v/v) starter culture (OD_{600} of 0.8). The cultures are shaken at 37°C and 200 rpm and grown to an OD_{600} of 0.6-0.8 followed by induction with 0.5mM IPTG at 15°C and 200 rpm for at least 10 hours or at 25°C for 4 hours.

The cells are harvested by centrifugation and the pellets are resuspended in 25 ml HEPES buffer (50 mM, pH 7.5), supplemented with 100μl of protease inhibitors (PMSF and benzamidine (Sigma)) and flash-frozen in liquid nitrogen.

Alternatively, for an unlabeled polypeptide of the invention, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 20 mL of medium having 47.6 g/L of Terrific Broth and 1.5% glycerol in dH_2O followed by autoclaving for 30 minutes at 121°C and 15 psi. When the broth cools to room temperature, the medium is supplemented with 6.3 μM $CoCl_2$-$6H_2O$, 33.2 μM $MnSO_4$-$5H_2O$, 5.9 μM $CuCl_2$-$2H_2O$, 8.1 μM H_3BO_3, 8.3 μM Na_2MoO_4-$2H_2O$, 7 μM $ZnSO_4$-$7H_2O$, 108 μM $FeSO_4$-$7H_2O$, 68 μM $CaCl_2$-$2H_2O$, 4.1 μM $AlCl_3$-$6H_2O$, 8.4 μM $NiCl_2$-$6H_2O$, 1 mM $MgSO_4$, 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 25 μg/mL Carbenicillin, and 50 μg/mL Kanamycin. The medium is then inoculated with several colonies of the freshly transformed expression construct of interest. The culture is incubated at 37°C and 260 rpm for about 3 hours and then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is then incubated at 37°C with shaking at 230-250 rpm on an orbital shaker having a 1 inch orbital diameter. When the culture reaches an OD_{600} of 3-6 it is induced with 0.5 mM IPTG. The induced culture is then incubated at 15°C with shaking at 230-250 rpm or faster for about 6-15 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 μl of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

EXAMPLE 3 Expression of Selmet Labeled Polypeptides

The freshly transformed cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 20 ml of NMM (New Minimal Medium) and shaken at 37°C for 8-9 hours. This culture is then transferred into a 6L Erlenmeyer flask containing 2L of minimum medium (M9). The media is supplemented with all amino acids except methionine. All amino acids are added as a solution except for Tyrosine, Tryptophan and Phenylalanine which are added to the media in powder format. As well the media is supplemented with $MgSO_4$ (2mM final concentration), $FeSO_4.7H_2O$ (25mg/L final concentration), Glucose (0.4% final concentration), $CaCl_2$ (0.1mM final concentration) and Seleno-L-Methionine (40mg/L final concentration). When the OD_{600} of the cell culture reaches 0.8-0.9, IPTG (0.4 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 15°C for 10 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (PMSF and Benzamidine) and flash frozen.

Alternatively, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 50 mL of sterile medium having 10% 10XM9 (37.4 mM NH_4Cl (Sigma; Cat. No. A4514), 44 mM KH_2PO_4 (Bioshop, Ontario, Canada; Cat. No. PPM 302), 96 mM Na_2HPO_4 (Sigma; Cat. No. S2429256), and 96 mM $Na_2HPO_4 \cdot 7H_2O$ (Sigma; Cat. No. S9390) final concentration), 450 µM alanine, 190 µM arginine, 302 µM asparagine, 300 µM aspartic acid, 330 µM cysteine, 272 µM glutamic acid, 274 µM glutamine, 533 µM glycine, 191 µM histidine, 305 µM isoleucine, 305 µM leucine, 220 µM lysine, 242 µM phenylalanine, 348 µM proline, 380 µM serine, 336 µM threonine, 196 µM tryptophan, 220 µM tyrosine, and 342 µM valine, 204 µM Seleno-L-Methionine (Sigma; Cat. No. S3132), 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 2 mM $MgSO_4$ (Sigma; Cat. No. M7774), 90 µM $FeSO_4 \cdot 7H_2O$ (Sigma; Cat. No. F8633), 0.4% glucose (Sigma; Cat. No. G-5400), 100 µM $CaCl_2$ (Bioshop, Ontario, Canada; Cat. No. CCL 302), 50 µg/mL Ampicillin, and 50 µg/mL Kanamycin in dH_2O. The medium is then inoculated with several colonies of *E. coli* B834 cells (Novagen) freshly transformed with an expression construct clone encoding the polypeptide of interest. The culture is then incubated at 37°C and 200 rpm until it reaches an OD_{600} of ~1 and is then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is incubated at 37°C

with shaking at 200 rpm until the culture reaches an OD_{600} of 0.6-0.8 and is then induced with 0.5 mM IPTG. The induced culture is incubated overnight at 15°C with shaking at 200 rpm. The cells are harvested by centrifugation at 4200 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

Alternatively, the cell harboring a plasmid with a nucleic acid encoding a polypeptide of the invention is inoculated into 10 ml of M9 minimum medium and kept shaking at 37°C for 8-9 hours. This culture is then transferred into a 2L Baffled Flask (Corning) containing 1L minimum medium. The media is supplemented with all amino acids except methionine. All are added as a solution, except for Phenylalanine, Alanine, Valine, Leucine, Isoleucine, Proline, and Tryptophan which are added to the media in powder format. As well the media is supplemented with $MgSO_4$ (2mM final concentrtion), $FeSO_4 \cdot 7H_2O$ (25 mg/L final concentration), Glucose (0.5% final concentration), $CaCl_2$ (0.1 mM final concentration) and Seleno-Methionine (50 mg/L final concentration). When the OD_{600} of the cell culture reaches 0.8-0.9, IPTG (0.8 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 25°C for 4 hours. The cells are harvested by centrifuged at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (PMSF and Benzamidine) and flash frozen.

EXAMPLE 4 Expression of ^{15}N Labeled Polypeptides

The cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 2L of minimal media (containing ^{15}N isotope, Cambridge Isotope Lab) in a 6L Erlenmeyer flask. The minimal media is supplemented with 0.01 mM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mg/L Thiamine.HCl, and 0.4% glucose. The 2L culture is grown at 37°C and 200 rpm to an OD_{600} of between 0.7-0.8. The culture is then induced with 0.5 mM IPTG and allowed to shake at 15°C for 14 hours. The cells are harvested by centrifugation and the cell pellet is resuspended in 15 mL cold binding buffer and 100µl of protease inhibitor and flash frozen. The protein is then purified as described below.

Alternatively, the freshly transformed cell, harboring a plasmid with the gene of interest, is inoculated into 10 mL of M9 media (with ^{15}N isotope) and supplemented with with 0.01 mM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mg/L Thiamine.HCl, and 0.4% glucose. After 8-10 hours of growth at 37°C, the culture is transferred to a 2L Baffled flask (Corning) containing 990 mL of the same media. When OD_{600} of the culture is between 0.7-0.8, protein production is initiated by adding IPTG to a final concentration of 0.8 mM and lowering the temperature to 25°C. After 4 hours of incubation at this temperature, the cells are harvested, and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitor and flash frozen.

EXAMPLE 5 Method One for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14,000 rpm for 60 min at 4°C to remove insoluble cellular debris. The supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Ni-NTA columns (Qiagen). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 25 ml of 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of binding buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 5 mM imidazole). Ni-NTA columns are prepared by adding 3.5-8 ml of resin to the column (20 mm wide, Biorad) based on the level of expression of the recombinant protein and equilibrating the column with 30 ml of binding buffer. The columns are arranged in tandem so that the protein sample is first passed over the DE52 column and then loaded directly onto the Ni-NTA column.

The Ni-NTA columns are washed with at least 150 ml of wash buffer (50mM HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 30 mM imidazole) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Ni-NTA column using elution buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 250 mM imidazole) until no more protein is observed in the aliquots of eluate as measured using Bradford reagent (Biorad). The eluate is supplemented with 1 mM of EDTA and 0.2 mM DTT.

The samples are assayed by SDS-PAGE and stained with Coomassie Blue, with protein purity determined by visual staining.

Two methods may be used to remove the His tag located at either the C or N-terminus. In certain instances, the His tag may not be removed. In either case, the expressed polypeptide will have additional residues attributable to the His tag, as shown in the following table:

SEQ ID NO for Additional Residues	*Additional Residues*	*Type of Tag and Whether or Not Removed*
N/A	GSH	His tag removed from N-terminus
SEQ ID NO: 7	MGSSHHHHHHSSGLVPRGSH	His tag not removed from N-terminus
SEQ ID NO: 8	GSENLYFQGHHHHHH	His tag removed from C-terminus
SEQ ID NO: 9	GSENLYFQ	His tag not removed from C-terminus

In method one, a sample of purified polypeptide are supplemented with 2.5 mM $CaCl_2$ and an appropriate amount of thrombin (the amount added will vary depending on the activity of the enzyme preparation) and incubated for ~20-30 minutes on ice in order to remove the His tag. In method two, a sample of purified polypeptide is combined with thirty units of recombinant TEV protease in 50 mmol TRIS HCl pH = 8.0, 0.5 mmol EDTA and 1 mmol DTT, followed by incubation at 4°C overnight, to remove the His tag.

The protein sample is then dialyzed in dialysis buffer (10mM HEPES, pH 7.5, 5% glycerol (v/v) and 0.5 M NaCl) for at least 8 hours using a Slide-A-Lyzer (Pierce) appropriate for the molecular weight of the recombinant protein. An aliquot of the cleaved and dialyzed samples is then assayed by SDS-PAGE and stained with Coomassie Blue to determine the purity of the protein and the success of cleavage.

The remainder of the sample is centrifuged at 2700 rpm at 4°C for 10-15 minutes to remove any precipitant and supplemented with 100 µl of protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) (NO Bioshop). The protein is then applied to a second Ni-NTA column (~8 ml of resin) to remove the His-tags and eluted with binding buffer or wash buffer until no more protein is eluting off the column as assayed using the Bradford reagent. The eluted sample is supplemented with 1 mM EDTA and 0.6 mM of DTT and concentrated to a final volume of ~15 mls using a Millipore Concentrator with an

appropriately sized filter at 2700 rpm at 4°C. The samples are then dialyzed overnight against crystallization buffer and concentrated to final volume of 0.3-0.7 ml.

EXAMPLE 6 Method Two for Purifying Polypeptides of the Invention

The frozen pellets are thawed and supplemented with 100 µl of protease inhibitor (0.1 M benzamidine and 0.05 M PMSF), 0.5% CHAPS, and 4 U/ml Benzonase Nuclease. The sample is then gently rocked on a Nutator (VWR, setting 3) at room temperature for 30 minutes. The cells are then lysed by sonication (1 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR) and an aliquot is saved for a gel sample.

The recombinant protein is purified using a three column system. The columns are set up in tandem so that the lysate flows from a Biorad Econo (5.0 x 30 cm x 589 ml) "lysate" column onto a Biorad Econo (2.5 x 20 cm x 98 ml) DE52 column and finally onto a Biorad Econo (1.5 x 15 cm x 27 ml) Ni-NTA column. The lysate is mixed with 10 g of equilibrated DE52 resin and diluted to a total volume of 300 ml with binding buffer. This mixture is poured into the first column which is empty. The remainder of the purification procedure is described in EXAMPLE 5 above.

EXAMPLE 7 Method Three for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14000 rpm for 60 min at 4°C to remove insoluble cellular debris. The supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Glutathione sepharose columns (Glutathione-Superflow resin, Clontech). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 20 ml of 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of loading buffer (50mM in HEPES, pH 7.5, 10% glycerol (v/v), 0.5 M NaCl, 1 mM EDTA, 1 mM DTT). Glutathione sepharose columns are prepared by adding 3 ml of resin to the column (20 mm wide, Biorad) and equilibrating the column with 30 ml of loading

buffer. The columns are arranged in tandem so that the protein sample is first passed over the DE52 column and then loads directly onto the Glutathione sepharose column.

The columns are washed with at least 150 ml of loading buffer supplemented with protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Glutathione sepharose column using elution buffer (20mM HEPES, pH 7.5, 0.5 M NaCl, 1 mM EDTA, 1 mM DTT; 25 mM glutathione (reduced form)) until no more protein is observed in the aliquots of eluate as measured using Biorad Bradford reagent.

The GST tag may be removed using thrombin or other procedures known in the art. The protein samples are then dialyzed into crystallization buffer (10 mM Hepes, pH 7.5, 500 mM NaCl) to remove free glutathione and assayed by SDS-PAGE followed by staining with Coomassie blue. Prior to use or storage, the samples are concentrated to final volume of 0.3-0.5 ml.

Using one or more of the methods described above, purified polypeptide having SEQ ID NO: 4 is obtained in a yield of approximately 49.3 per liter of culture. The purified polypeptide is essentially the only protein visualized in the SDS-PAGE assay using Coomassie Blue described above, which is at least about 95% or greater purity. The polypeptide so expresssed and purified is His tagged (having sequence MGSSHHHHHHSSGLVPRGSH as described above) at the N-terminus.

Using one or more of the methods described above, purified selmet labeled polypeptide having SEQ ID NO: 4 is obtained in a yield of approximately 45.8 mg per liter of culture. The purified polypeptide is essentially the only protein visualized in the SDS-PAGE assay using Coomassie Blue described above, which is at least about 95% or greater purity. The polypeptide so expresssed and purified is His tagged (having sequence MGSSHHHHHHSSGLVPRGSH) at the N-terminus.

The protein samples so prepared and purified may be used in the biophysical studies that follow, with or without the His tag or the residual amino acids resulting from removal of the His tag. In certain instances, such as EXAMPLE 10, the polypeptide used may be a fusion protein with a specific tag.

A stable solution of purified polypeptide having SEQ ID NO: 4, prepared and purified as described above, may be prepared with 123.2 mg (or a lesser amount) of protein

in one ml of either the dialysis or crystallization buffers (or possibly both) described above in EXAMPLE 5 or EXAMPLE 7, respectively.

A stable solution of purified selmet labeled polypeptide having SEQ ID NO: 4, prepared and purified as described above, may be prepared with 91.6 mg (or a lesser amount) of protein in one ml of either the dialysis or crystallization buffers (or possibly both) described above in EXAMPLE 5 or EXAMPLE 7, respectively.

Certain of the foregoing information is also set forth in Table 1 of FIGURE 6.

EXAMPLE 8 Mass Spectrometry Analysis via Fingerprint Mapping

A gel slice from a purification protocol described above containing a polypeptide of the invention is cut into 1 mm cubes and 10 to 20 µl of 1% acetic acid is added. After washing with 100 - 150 µl HPLC grade water and removal of the liquid, acetonitrile (~200 µl, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may be required to completely dehydrate the gel particles. The protein in the gel particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) and then alkylated at room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium bicarbonate). The gel particles are rinsed with a minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM $CaCl_2$, and 12.5 ng/µl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 µl digestion buffer without trypsin is added to ensure the gel particles remain hydrated during digestion. After digestion at 37°C, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 µL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

The tryptic peptides are purified with a C18 reverse phase resin. 250 µL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1 slurry of solvent:resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 µL of the resin slurry is added and the solution is shaken for 30 minutes at room

temperature. The supernatant is removed and replaced with 200 µL of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes. The supernatant is removed and the peptides are eluted from the resin with 15 µL of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged, and the filtrate is collected and stored at –70°C until use.

Alternatively, the tryptic peptides are purified using ZipTip$_{C18}$ (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic (5 times) and returned to 2% acetonitrile/1% acetic acid (10 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 µL of 65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitre plate.

Analytical samples containing tryptic peptides are subjected to MALDI-TOF mass spectrometry. Samples are mixed 1:1 with a matrix of α-cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot, either a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is conducted using both delayed extraction mode (400 ns delay) and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against databases using a correlative mass matching algorithm. The Proteometrics software package (ProteoMetrics) is utilized for batch database searching of tryptic peptide mass spectra. Statistical analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, carboxyamidomethylation of cysteines, no oxidation of methionines allowed, and 0 or 1 missed enzyme cleavages. The software calculates the probability that a candidate in the database search is the protein being analyzed, which is expressed as the Z-score. The Z-score is the distance to the population mean in unit of standard deviation and corresponds to the percentile of the search in the random match population. If a search is in the 95th percentile, for example, about 5% of random matches could yield a higher Z-score than the

search. A Z-score of 1.282 for a search indicates that the search is in the 90th percentile, a Z-score of 1.645 indicates that the search is in the 95th percentile, a Z-score of 2.326 indicates that the search is in the 99th percentile, and a Z-score of 3.090 indicates that the search is in the 99.9th percentile.

EXAMPLE 9 Mass Spectrometry Analysis via High Mass

A matrix solution of 25 mg/mL of 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid) in 66% (v/v) acetonitrile/1% (v/v) acetic acid is prepared along with an internal calibrant of carbonic anhydrase. On to a stainless steel polished MALDI target, 1.5 µL of a protein solution (concentration of 2 µg/µL) is spotted, followed immediately by 1.5 µL of matrix. 3 µL of 40% (v/v) acetonitrile/1% (v/v) acetic acid is then added to each spot has dried. The sample is either spotted manually or utilizing a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The MALDI-TOF instrument utilizes positive ion and linear detection modes. Spectra are acquired automatically over a mass to charge range from 0-150,000 Da, pulsed ion extraction delay is set at 200 ns, and 600 summed shots of 50-shot steps are completed.

The theoretical molecular weight of the protein for MALDI-TOF is determined from its amino acid sequence, taking into account any purification tag or residue thereof still present and any labels (e.g., selenomethionine or ^{15}N). To account for ^{15}N incorporation, an amount equal to the theoretical molecular weight of the protein divided by 70 is added. The mass of water is subtracted from the overall molecular weight. The MALDI-TOF spectrum is calibrated with the internal calibrant of carbonic anhydrase (observed as either $[MH^{+}_{avg}]$ 29025 or $[MH_2^{2+}]$ 14513).

EXAMPLE 10 Method One for Isolating and Identifying Interacting Proteins

(a) Method One for Preparation of Affinity Column

Micro-columns are prepared using forceps to bend the ends of P200 pipette tips and adding 10 µl of glass beads to act as a column frit. Six micro-columns are required for every polypeptide to be studied. The micro-columns are placed in a 96-well plate that has 1 mL wells. Next, a series of solutions of the polypetide having SEQ ID NO: 4 or other polypeptide of the invention, prepared and purified as described above and with a GST tag

on either terminus, is prepared so as to give final amounts of 0, 0.1, 0.5, 1.0, and 2.0 mg of ligand per ml of resin volume.

A slurry of Glutathione-Sepharose 4B (Amersham) is prepared and 0.5 ml slurry/ligand is removed (enough for six 40-μg aliquots of resin). Using a glass frit Buchner funnel, the resin is washed sequentially with three 10 ml portions each of distilled H_2O and 1 M ACB (20 mM HEPES pH 7.9, 1 M NaCl, 10% glycerol, 1 mM DTT, and 1 mM EDTA). The Glutathione-Sepharose 4B is completely drained of buffer, but not dried. The Glutathione-Sepharose 4B is resuspended as a 50% slurry in 1 M ACB and 80 μl is added to each micro-column to obtain 40 μg/column. The buffer containing the ligand concentration series is added to the columns and allowed to flow by gravity. The resin and ligand are allowed to cross-link overnight at 4°C. In the morning, micro-columns are washed with 100 μl of 1 M ACB and allowed to flow by gravity. This is repeated twice more and the elutions are tested for cross-linking efficiency by measuring the amount of unbound ligand. After washing, the micro-columns are equilibrated using 200 μl of 0.1 M ACB (20 mM HEPES pH 7.5, 0.1 M NaCl, 10% glycerol, 1 mM DTT, 1 mM EDTA).

In another method, the recombinant GST fusion protein can be replaced by a hexa-histidine fusion peptide for use with NTA-Agarose (Qiagen) as the solid support. No adaptation to the above protocol is required for the substitution of NTA agarose for GST Sepharose except that the recombinant protein requires a six histidine fusion peptide in place of the GST fusion.

(b) Method Two for Preparation of Affinity Column

In an alternative method, GST-Sepharose 4B may be replaced by Affi-gel 10 Gel (Bio-Rad). The column resin for affinity chromatography could also be Affigel 10 resin which allows for covalent attachment of the protein ligand to the micro affinity column. An adaptation to the above protocol for the use of this resin is a pre-wash of the resin with 100% isopropanol. No fusion peptides or proteins are required for the use of Affigel 10 resin.

(c) Method One for Bacterial Extract Preparation

A *P. aeruginosa* extract is prepared from cell pellets using a French press followed by sonication. An *P. aeruginosa* cell pellet (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM $MgSO_4$, 10

mM $CaCl_2$, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 μg/ml RNAse A, 75 units/ml S1 nuclease, and 40 units/ml DNAse 1. The cell suspension is lysed with one pass with a French Pressure Cell followed by sonication on ice using three bursts of 20 seconds each. The lysate is agitated at 4°C for 30 minutes, brought up to 0.5 M NaCl and then incubated for an additional 30 min at 4°C with agitation. The lysate is centrifuged at 25,000 rpm for 1 hr at 4°C in a Ti70 fixed angle Beckman rotor. The supernatant is removed and dialyzed overnight in a 10,000 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at –70°C.

(d) Method Two for Bacterial Extract Preparation

Bacterial cell extracts from *P. aeruginosa* are prepared from cell pellets using a Bead-Beater apparatus (Bio-spec Products Inc.) and zirconia beads (0.1 mm diameter). The bacterial cell pellet is suspended (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 μg/ml RNAse A, 75 units/ml S1 nuclease, and 40 units/ml DNAse 1. The cells are lysed with 10 pulses of 30 sec between 90 sec pauses at a temperature of -5 °C. The lysate is separated from the zirconia beads using a standard column apparatus. The lysate is centrifuged at 20000 rpm (48000 x g) in a Beckman JA25.50 rotor. The supernatant is removed and dialyzed overnight at 4 °C against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM $MgSO_4$, 10 mM $CaCl_2$, 1 mM benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at -70°C.

(e) HeLa Cell Extract Preparation

A HeLa cell extract is prepared in the presence of protease inhibitors. Approximately 30 g of Hela cells are submitted to a freeze/thaw cycle and then divided into two tubes. To each tube 20 ml of Buffer A (10 mM HEPES pH 7.9, 1.5 mM MgCl, 10 mM KCl, 0.5 mM DTT, 0.5 mM PMSF) and a protease inhibitor cocktail are added. The cell suspension is homogenized with 10 strokes (2 x 5 strokes) to lyse the cells. Buffer B (15 ml per tube) is added (50 mM HEPES pH 7.9, 1.5 mM MgCl, 1.26 M NaCl, 0.5 mM DTT, 0.5 mM PMSF, 0.5 mM EDTA, 75% glycerol) to each tube followed by a second round of homogenization (2 x 5 strokes). The lysates are stirred on ice for 30 minutes followed by

centrifugation 37,000 rpm for 3 hr at 4°C in a Ti70 fixed angle Beckman rotor. The supernatant is removed and dialyzed overnight in a 10,000 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.9, 10 % glycerol, 1 mM DTT, 1 mM EDTA, and 1 M NaCl. The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at –70°C.

(f) Affinity Chromatography

Cell extract is thawed and diluted to 5 mg/ml prior to loading 5 column volumes onto each micro-column. Each column is washed with 5 column volumes of 0.1 M ACB. This washing is repeated once. Each column is then washed with 5 column volumes of 0.1 M ACB containing 0.1% Triton X-100. The columns are eluted with 4 column volumes of of 1% sodium dodecyl sulfate into a 96 well PCR plate. To each eluted fraction is added one-tenth volume of 10-fold concentrated loading buffer for SDS-PAGE.

(g) Resolution of the Eluted Proteins and Detection of Bound Proteins

The components of the eluted samples are resolved on SDS-polyacrylamide gels containing 13.8% polyacrylamide using the Laemmli buffer system and stained with silver nitrate. The bands containing the interacting protein are excised with a clean scalpel. The gel volume is kept to a minimum by cutting as close to the band as possible. The gel slice is placed into one well of a low protein binding, 96-well round-bottom plate. To the gel slices is added 20 µl of 1% acetic acid.

EXAMPLE 11 Method Two for Isolating and Identifying Interacting Proteins

Interacting proteins may be isolated using immunoprecipitation. Naturally-occurring bacterial or eukaryotic cells are grown in defined growth conditions or the cells can be genetically manipulated with a protein expression vector. The protein expression vector is used to transiently transfect the cDNA of interest into eukaryotic or prokaryotic cells and the protein is expressed for up to 24 or 48 hours. The cells are harvested and washed three times in sterile 20 mM HEPES (pH7.4)/Hanks balanced salts solution (H/H). The cells are finally resuspended in culture media and incubated at 37°C for 4-8 hr.

The harvested cells may be subjected to one or more culture conditions that may alter the protein profile of the cells for a given period of time. The cells are collected and washed with ice-cold H/H that includes 10 mM sodium pyrophosphate, 10 mM sodium

fluoride, 10mM EDTA, and 1mM sodium orthovanadate. The cells are then lysed in lysis buffer (50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Triton X-100, 10 mM sodium pyrophosphate, 10mM sodium fluoride, 10mM EDTA, 1mM sodium orthovanadate, 1ug/mL PMSF, 1ug/mL aprotinin, 1ug/mL leupetin, and 1ug/mL pepstatin A) by gentle mixing, and placed on ice for 5 minutes. After lysis, the lysate is transferred to centrifuge tubes and centrifuged in an ultracentrifuge at 75000 rpm for 15 min at 4°C. The supernatant is transferred to eppendorf tubes and pre-cleared with 10 µl of rabbit pre-immune antibody on a rotator at 4°C for 1 hr. Forty µl of protein A-Sepharose (Amersham) is then added and incubated at 4°C overnight on a rotator.

The protein A-Sepharose beads are harvested and the supernatant removed to a fresh eppendorf tube. Immune antibody is added to supernatant and rotated for 1 hr at 4°C. Thirty µl of protein A-Sepharose is then added and the mixture is further rotated at 4°C for 1 hr. The beads are harvested and the supernatant is aspirated. The beads are washed three times with 50 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Triton X-100, 10 mM sodium fluoride, 10 mM sodium pyrophosphate, 10 mM sodium orthovanadate, and 10 mM EDTA. Dry the beads with a 50 µl Hamilton syringe. Laemmli loading buffer containing 100 mM DTT is added to the beads and samples are boiled for 5 min. The beads are spun down and the supernatant is loaded onto SDS-PAGE gels. Comparison of the control and experimental samples allows for the selection of polypeptides that interact with the protein of interest.

EXAMPLE 12 Sample for Mass Spectrometry of Interacting Proteins

The gel slices are cut into 1 mm cubes and 10 to 20 µl of 1% acetic acid is added. The gel particles are washed with 100 - 150 µl of HPLC grade water (5 minutes with occasional mixing), briefly centrifuged, and the liquid is removed. Acetonitrile (~200 µl, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may be required to completely dehydrate the gel particles. The sample is briefly centrifuged and all the liquid is removed.

The protein in the gel particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) for 30 minutes and then alkylated at

room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium bicarbonate). The gel particles are rinsed with a minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM $CaCl_2$, and 12.5 ng/µl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 µl digestion buffer without trypsin is added to ensure the gel particles remain hydrated during digestion. The samples are digested overnight at 37°C.

The following day, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 µL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

(a) Method One for Purification of Tryptic Peptides

The tryptic peptides are purified with a C18 reverse phase resin. 250 µL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1 slurry of solvent : resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 µL of the resin slurry is added and the solution is shaken at moderate speed for 30 minutes at room temperature. The supernatant is removed and replaced with 200 µL of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes with moderate speed. The supernatant is removed and the peptides are eluted from the resin with 15 µL of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged for 1-2 minutes at 1000 rpm, the filtrate is collected and stored at –70°C until use.

(b) Method Two for Purification of Tryptic Peptides

Alternatively, the tryptic peptides may be purified using $ZipTip_{C18}$ (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol 5 times. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic (5 times) and returned to 2% acetonitrile/1% acetic acid (5 times). The ZipTips are replaced in their rack and the residual solvent is eliminated. The ZipTips are washed again with 2% acetonitrile/1% acetic acid (5 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 µL of

65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitire plate. 1 μL of sample and 1 μL of matrix are spotted on a MALDI-TOF sample plate for analysis.

EXAMPLE 13 Mass Spectrometric Analysis of Interacting Proteins

(a) Method One for Analysis of Tryptic Peptides

Analytical samples containing tryptic peptides are subjected to Matrix Assisted Laser Desorption/Ionization Time Of Flight (MALDI-TOF) mass spectrometry. Samples are mixed 1:1 with a matrix of α-cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot. The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is conducted using both delayed extraction mode and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against both in-house proprietary and public databases using a correlative mass matching algorithm. Statistical analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses and carboxyamidomethylation of cysteines. Identified proteins are stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences.

(b) Method Two for Analysis of Tryptic Peptides

Alternatively, samples containing tryptic peptides are analyzed with an ion trap instrument. The peptide extracts are first dried down to approximately 1 μL of liquid. To this, 0.1% trifluoroacetic acid (TFA) is added to make a total volume of approximately 5 μL. Approximately 1-2 μL of sample are injected onto a capillary column (C8, 150 μm ID, 15 cm long) and run at a flow rate of 800 nL/min. using the following gradient program:

Time (minutes)	% Solvent A	% Solvent B
0	95	5
30	65	35
40	20	80
41	95	5

Where Solvent A is composed of water/0.5% acetic acid and Solvent B is acetonitrile/0.5% acetic acid. The majority of the peptides will elute between the 20-40 %

acetonitrile gradient. Two types of data from the eluting HPLC peaks are acquired with the ion trap mass spectrometer. In the MS^1 dimension, the mass to charge range for scanning is set at 400-1400 - this will determine the parent ion spectrum. Secondly, the instrument has MS^2 capabilities whereby it will acquire fragmentation spectra of any parent ions whose intensities are detected to be greater than a predetermined threshold (Mann and Wilm, *Anal Chem* 66(24): 4390-4399 (1994)). A significant amount of information is collected for each protein sample as both a parent ion spectrum and many daughter ion spectra are generated with this instrumentation.

All resulting mass spectra are submitted to a database search algorithm for protein identification. A correlative mass algorithm is utilized along with a statistical verification of each match to identify a protein's identification (Ducret A, et al., *Protein Sci* 7(3): 706-719 (1998)). This method proves much more robust than MALD-TOF mass spectrometry for identifying the components of complex mixtures of proteins.

No interacting proteins were observed using at least one of the methods described above.

EXAMPLE 14 NMR Analysis

Purified protein sample is centrifuged at 13,000 rpm for 10 minutes with a bench-top microcentrifuge to eliminate any precipitated protein. The supernatant is then transferred into a clean tube and the sample volume is measured. If the sample volume is less than 450 µl, an appropriate amount of crystal buffer is added to the sample to reach that volume. Then 50 µl of D_2O (99.9%) is added to the sample to make an NMR sample of 500 µl. The usual concentration of the protein sample is usually approximately 1 mmol or greater.

NMR screening experiments are performed on a Bruker AV600 spectrometer equipped with a cryoprobe, or other equivalent instrumentation. All spectra are recorded at 25°C. Standard 1D proton pulse sequence with presaturation is used for 1D screening. Normally, a sweepwidth of 6400 Hz, and eight or sixteen scans are used, although different pulse sequences are known to those of skill in the art and may be readily determined. For ^1H, ^{15}N HSQC experiments, a pulse sequence with "flip-back" water suppression may be used. Typically, sweepwidths of 8000 Hz and 2000 Hz are used for F2 and F1 dimension,

respectively. Four to sixteen scans are normally adequate. The data is then processed on a Sun Ultra 5 computer with NMRpipe software.

EXAMPLE 15 X-ray Crystallography

(a) Crystallization

Subsequent to purification, a subject polypeptide is centrifuged for 10 minutes at 4°C and at 14,000 rpm in order to sediment any aggregated protein. The protein sample is then diluted in order to provide multiple concentrations for screening.

Two 96 well plates (Nunc) are employed for the initial crystal screen, with 48 potential crystallization conditions. The screening library has crystallization conditions found in Hampton Research Crystal Screen I (Jankarik, J. and S.H. Kim, J. Appl. Cryst., 1991. 24:409-11), Hampton Research Crystal Screen II, Hampton Crystal Screen I-Lite, and from Emerald Biostructures, Inc., Bainbridge Island, WA, Wizard I, Wizard II, Cryo I and Cryo II. Alternatively, other conditions known to those of skill in the art, including those provided in screening kits available from other companies, may also be tested.

Conditions are tested at multiple protein concentrations and at two temperatures (4 and 20°C). Crystal setups may be performed by a liquid handling robot appropriately programmed for sitting drop experiments. The robot loads 50 µl of buffer into each screening well on a 24 or 96 well sitting drop crystal screen tray, and then loads 1 - 5 µl of protein into each drop reservoir to be screened on the plate. Subsequently, the robot loads 1.5 µl of the corresponding screening solution into the drop reservoir atop the protein. The plate is then sealed using transparent tape, and stored at 4 or 20°C. Each plate is observed two days, two weeks, and 1 month after being set. Alternatively, screens may be performed using 0.1 - 10 µl drops suspended at the interface of two immiscible oils. The protein containing solution has a density intermediate between the two oils and thus floats between them (Chayen N.E.: 1996, *Protein Eng.* 9:927–29). This procedure may be performed in an automated fashion by an appropriately programmed liquid handling robot, with additional steps being required initially to introduce the oils. No tape is added to facilitate gradual drying out of the drop to promote crystallization.

Having identified conditions that are best suited for further crystal refinement, subsequent plates are set up to explore the affects of variables such as temperature, pH, salt

or PEG concentration on crystal size and form, with the intent of establishing conditions where the protein is able to form crystals of suitable size and morphology for diffraction analysis. Each refinement is performed in the sitting drop format in a 24 well Lindbro plate. Each well in the tray contains 500 µl of screening solution, and a 1.5 µl drop of protein diluted with 1.5 µl of the screening solution is set to hang from the siliconized glass cover slip covering the well. Alternatively, refinement steps may be performed using either the machine 96 well plate hanging drop method or the oil suspension method described above.

Crystals of a selenomethionine-substituted polypeptide having the sequence of SEQ ID NO: 4, prepared and purified as described above and having a His tag, are obtained using the following conditions: 30% MPD, 0.1M sodium acetate pH 4.6, 20mM calcium chloride. In addition, crystals of the same polypeptide may be prepared under the following conditions: 0.4M potassium sodium tartrate. Further, crystals of the same polypeptide may be prepared under the following conditions: 30% PEG 4000, 0.1M TRIS pH 8.5, 0.2M magnesium chloride. Further, crystals of the same polypeptide may be prepared under the following conditions: 35% PEG 400, 0.2M Tris-HCl, pH 8.5, trisodium citrate dihydrate. The crystals were prepared using the following method: 20°C, sitting-drop, 10 mg/mL.

(b) Co-Crystallization

A variety of methods known in the art may be used for preparation of co-crystals comprising the subject polypeptides and one or more compounds that interact with the subject polypeptides, such as, for example, an inhibitor, co-factor, substrate, polynucleotide, polypeptide, and/or other molecule. In one exemplary method, crystals of the subject polypeptide may be soaked, for an appropriate period of time, in a solution containing a compound that interacts with a subject polypeptide. In another method, solutions of the subject polypeptide and/or compound that interacts with the subject polypeptide may be prepared for crystallization as described above and mixed into the above-described sitting drops. In certain embodiments, the molecule to be co-crystallized with the subject polypeptide may be present in the buffer in the sitting drop prior to addition of the solution comprising the subject polypeptide. In other embodiments, the subject polypeptide may be mixed with another molecule before adding the mixture to the sitting drop. Based on the teachings herein, one of skill in the art may determine the co-crystallization method yielding a co-crystal comprising the subject polypeptide.

(c) Heavy Atom Substitution

For preparation of crystals containing heavy atoms, crystals of the subject polypeptide may be soaked in a solution of a compound containing the appropriate heavy atom for such period as time as may be experimentally determined is necessary to obtain a useful heavy atom derivative for x-ray purposes. Likewise, for other compounds that may be of interest, including, for example, inhibitors or other molecules that interact with the subject polypeptide, crystals of the subject polypeptide may be soaked in a solution of such compound for an appropriate period of time.

(d) Data collection and processing

Crystals of TpiA (selenomethionyl) from *P. aeruginosa* were obtained at room temperature by the sitting drop vapour diffusion method in Tris-HCl (pH 8.5), 35% (vol/vol) PEG 400, and 0.2 M Trisodium Citrate Dihydrate. A suitable diamond-shaped crystal of TpiA (dimensions approx. 300 x 100 x 100 mm) was selected for structure determination by single-crystal X-ray diffraction methods. The crystal in 20% ethylene glycol was frozen (100 K) in a nitrogen cold stream (Oxford Cryostream system) and diffraction data were collected at the Advanced Photon Source (Argonne National Laboratory) using the COM-CAT beamline equipped with a MAR CCD detector. The raw data were analyzed and reduced with the DENZO/SCALEPACK package. The protein was observed to crystallize in the hexagonal space group $P6_1$ with a = 77.349, c = 175.528 Å, and 2 molecules per asymmetric unit. Phase calculations, density modification and refinement were carried out using the CNX suite of programs. The coordinates from the structure of *E. coli* TIM (PDB ID #1TRE) were used as a starting model for phasing. Rigid body refinement was followed by refinement by maximum likelihood refinement against structure factors. The structure was partially built automatically by MAID, and completed manually by tracing the polypeptide chain in Turbo-Frodo. Refinement was performed in CNX, using simulated annealing torsion angle dynamics and individual B-factor refinement against maximum likelihood targets. Water molecules were automatically picked in CNX, and confirmed by visual inspection. A final inspection of $2|Fo|-|Fc|\alpha c$ and $|Fo|-|Fc|\alpha c$ maps were used to locate all remaining ordered solvent molecules. Several iterations of model rebuilding in Turbo-Frodo and subsequent refinements were performed until convergence was achieved.

Structure solution and refined statistics are reported in Table 3, contained in FIGURE 8. FIGURE 9 contains a list of the atomic coordinates of the subject polypeptide and other molecules contained in the crystal. FIGURE 10 to FIGURE 16 depict various features of the crystal structure and other properties of a subject polypeptide.

(e) Analysis of the X-ray Structure of the Subject Polypeptide

General Description of Structure

P. aeruginosa triosephosphate isomerase (TIM) adopts a three-dimensional structure similar to other known TIM architectures. It is a homodimer consisting of two almost identical subunits. The monomer, consisting of 250 residues, is a single domain that can be described as an α/β barrel (or β barrel) due to the organization of its 8 $\alpha\beta$ units. The 8 β strands are aligned parallel to each other, forming a cylindrical inner structure (the "barrel") whose side is decorated by the adjoining α helices via the corresponding loops (FIGURE 11 and FIGURE 12). The common occurrence of this structure in numerous triosephosphate isomerases has resulted in the coinage of the more fitting description "TIM barrel". The geometric parameters of β barrels include the strand number ($n = 8$), the tilt of the β strands relative to the barrel axis (~ 36°), and the radius of the barrel (~ 6.5 – 7.5 Å, depending on the eccentricity of the cross-section).

Active Site and Other Druggable Regions

Structurally, the active site appears to lie near the top of the TIM barrel towards the C-terminal ends of the β strands. The participating residues in the proton transfer reactions at the active site include the base Glu165 and acid His95 (amino acid numbering convention according to enzyme from chicken muscle). As shown in FIGURE 13 for *S. cerevisiae* TIM complexed with the transition state analogue 2-phosphoglycolytic acid, the other pertinent but non-catalytic residues at the active site appear to include Asn10 and Lys12, which may play a key role in anchoring the substrate at the catalytic site by binding its phosphate moiety via hydrogen bonds. Moreover, the positively charged side chain of Lys12 appears to help electrostatically stabilize the negatively charged transition state. The active site of *P. aeruginosa* TIM, comprising residues Glu165, His95, Asn10, and Lys12, and the surrounding residues, may present a druggable region.

During glycolysis, it is believed that the active site of TIM may accommodate either glyceraldehyde 3-phosphate or dihydroxyacetone phosphate, the interconversion of which

is thought to proceed via an unstable enediol intermediate. Thus, the enzyme appears to play an important role in both promoting the proton exchange to the form the enediol as well as stabilizing the intermediate. Analyses of TIM structures with and without inhibitory substrates bound have revealed an 11-residue (residues 166 – 176) flexible loop that, upon binding of a substrate, is believed to close over the active site. This conformational change involves main chain shifts of > 7 Å as well as bringing the carboxylate group of the catalytic Glu165 approximately 2 Å toward the substrate from its position in the unbound enzyme. During such proposed closure of the flexible loop, the hydroxyl group of the residue Tyr208 may form a hydrogen bond with the amide nitrogen of Ala176. Loop closure appears to be essential for shielding the active site from water and stabilizing the charged enediol transition state. The transition state, which normally decomposes in solution to form the toxic end product methylglyoxal, appears to be stabilized because the loop closure prevents the phosphate elimination reaction of the substrate. The open and closed conformations of the TIM structure are shown in FIGURE 14 and FIGURE 15.

The flexible loop appears to be a fairly conserved region of the enzyme, but variations have been observed between the yeast TIM sequence and the organisms of FIGURE 10. For example, position 175 is an alanine residue in yeast, but is a threonine residue in *P. aeruginosa*, and a serine residue in *E. coli*, *H. pylori*, *S. aureus*, *S. pneumoniae*, and *E. faecalis*. The loop in *P. aeruginosa* TIM enzyme comprising residues Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176, may present a druggable region. The region closed off by and surrounding the loop may also may present a druggable region.

As shown in FIGURE 16, the active site involved in glycolysis in TIM structures is generally a conserved region of the enzyme. Thus, identifying inhibitors that bind to the active site of one TIM enzyme and not another may prove challenging. Other regions of the enzyme are under investigation for potential druggable regions that are more varied, including a region of significant differences between the trypanosomal (Ala100–Tyr101–Tyr102) and human (His100–Val101–Phe102) TIM enzymes, which is located approximately 15 Å from the entrance to the true active site. In *P. aeruginosa* TIM enzyme, the catalytic center region is comprised of Leu100, Ile101, and Leu102, and may present a druggable region.

The structure of *T. cruzi* TIM (TcTIM) cocrystallized with hexane revealed three substrate molecules (H1,H2, H3) bound on the surface of TcTIM at regions that, in the

native structure, do not contain water molecules. One hexane molecule (H1) resides at < 4 Å from residues Arg135, Thr140, and Glu186 (part of loop 5 and helix 6) of subunit B. The other two, separated by 3.8 Å, are found in a hydrophobic patch composed of residues from both subunits: H2 is < 4 Å from Ile69, Tyr103, Gly104, Ile109, and Lys113 of subunit A and from Tyr102 and Tyr103 of subunit B. Similarly, H3 is found at < 4 Å from Phe75 (subunit A) and Tyr102 and Tyr103 (subunit B). The bound hexane molecules were observed to change the orientation of the side chain of the catalytic Glu residue compared to the native form, a long-range effect which could influence the catalytic activity of the complexed TIM. Of further interest is the proximity of H2 and H3 to the residues Ile69 and Phe75, which both belong to loop 3 (69 – 80) of subunit A. The regions in *P. aeruginosa* TIM that correspond to the first, second, and third hexane-binding regions are comprised of residues Arg134, Thr139, and Glu185 for the first hexane; Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102 for the second hexane; and Leu74, Ile101, and Leu102 for the third hexane. These regions all present druggable regions.

It has been reported that the interactions of loop 3 from one subunit with residue 15 from the other subunit are important in dimer stability and enzyme catalysis. Selective inhibition of TcTIM Cys15 by sulfhydryl reagents at concentrations which do not affect human TIM (which has a Met at residue 15) or those lacking a cysteine in position 15 has been reported. Although in *P. aeruginosa* TIM this position is occupied by Met, the surrounding interdimer interface region of TIM nevertheless represents a druggable region, as there are 58 residues that participate in the intersubunit contacts of TIM. FIGURE 17 contains Table 4, which lists the residues in the intersubunit region of TcTIM (*T. cruzi* TIM), PaTIM (*P. aeruginosa* TIM), and HsTIM (*H. sapiens* TIM).

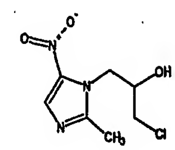
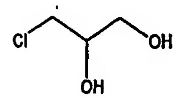
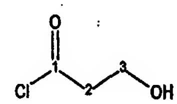
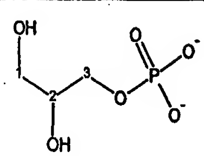
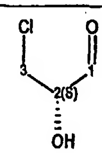
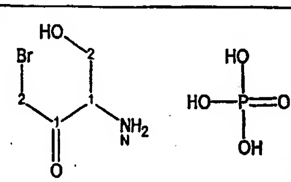
A comparison of the intersubunit residues in TcTIM, PaTIM, and humanTIM (listed in Table 4 of FIGURE 17) reveals that a unique Cys43 is found in PaTIM. This site may present a potential target residue for sulfhydryl agents or other drugs. There is also another unique cysteine (Cys88) which could be a potential target for such agents. FIGURE 18 depicts the location of these residues along the intersubunit interface. There are other residues that appear unique to PaTIM. For example, the polar, hydrophilic Gln48 is found in PaTIM, while in humanTIM the corresponding residue is the hydrophobic Phe50, and in TcTIM the nonpolar Met51. Likewise, a glutamine residue appears at position 82 in PaTIM, while the corresponding positions in TcTIM and human TIM are nonpolar, hydrophobic residues isoleucine and methionine, respectively. The differences in charge

and hydrophobicity in regions surrounding such distinct residues may be exploited in designing a drug that uniquely targets PaTIM. Thus, unique intersubunit residues and the area surrounding them may present druggable regions.

Known Inhibitors of Triosephosphateisomerase (TIM) Enzymes

Several known inhibitors of TIM enzymes are depicted in Figure 19:

Figure 19

Inhibitor Name	Structure
(R,S)-ornidazole	
(R,S)-alpha-chlorohydrin	
1-chloro-3-hydroxypropanone	
D-glycerol 3-phosphate	
(S)-3-chlorolactaldehyde	
Bromoacetylethanolamine phosphate	

Other inhibitors include bromohydroxyacetone phosphate, glycidol phosphate, 2-phosphoglycolate, 2-phosphoglycolohydroxamate, 3-phosphopropionic acid, and 2-(N-formyl-N-hydroxy)-aminoethyl phosphonate.

The crystal structures of malarial TIM, Trypanosoma cruzi, Plasmodium falciparum, have been used in structure-based drug design efforts to discover antiparasitic agents. Since many parasites lack a functional tricarboxylic acid cycle, glycolysis is the sole energy source, making TIM an attractive target for antiprotozoal therapy.

Comparison to Other TIM enzymes

All TIM enzymes discovered to date have a TIM barrel structure. The TIM barrel consists of a cylinder composed of beta sheets surrounded by a rosette of alpha-helices. The catalytic mechanism of TIM action is still under active investigation, and the following discussion is not intended to be limiting in any way. These investigations have resulted in the following general findings: (1) TIM is active only as a dimer; (2) the structures of the two subunits are nearly identical, except at the two amino-terminal ends; (3) upon substrate binding, an 11-residue loop moves ~7 Å as a "lid" to close over the active site and the carboxylate group of the catalytic E165 moves ~2 Å toward the substrate from its position in the unbound enzyme. This motion has been deduced from many enzyme sources (chicken, trypanosome), as well as using various known enzyme inhibitors (phosphoglycolohydroxamate, 2-phosphoglycolate, 3-chloroacetol phosphate). The current hypothesis for the catalytic mechanism is an acid/base reaction in which E165 and H95 residues participate directly in proton transfer, in what is believed to be a concerted general acid – base catalysis involving low barrier hydrogen bonds. Other key residues are K12, Y208, and the 11-residue loop (aa 166-176). Wild-type triosephosphate isomerases appear to be active only as a dimer, although the enzyme is not cooperative.

Mutagenesis Studies

Site-directed mutagenesis of Glu165 to Asp165 in triosephosphate isomerase had the apparent effect of withdrawing the catalytic carboxylate group slightly away (~ 1 Å) from the substrate compared to its position in the native non-complexed conformation. The resulting deleterious effect on the activity of the mutant enzyme was reflected in the drastic decrease in the turnover (kcat) by 1000-fold. This experiment suggest that the glutamate residue in the active site is essential for full activity. Lys12 is believed to play a key role during substrate binding by fixing it in place in order for acid/base catalysis to occur.

When the Lys is replaced by Met in the K12M structure, the inhibitor PGH does not bind to the mutant isomerase, resulting in an open conformation of the enzyme

Based in part on the structural information described above, in one aspect, the present invention is directed towards druggable regions of a subject polypeptide or other TIM enzyme comprising the majority of the amino acid residues contained in a subject druggable region. In another aspect, the present invention is directed toward an inhibitor that interacts with the active site of such an enzyme. In another aspect, the present invention is directed towards an inhibitor that interacts with the flexible loop of such an enzyme so as to preclude it from closing, thereby inhibiting such enzyme. In still another aspect, the present invention is directed towards an inhibitor that interacts with the catalytic lid of such as enzyme so as to maintain the loop in the closed position. In yet another aspect, the present invention is directed towards an inhibitor that binds in the region that becomes closed off by the loop, and may optionally interact with the loop when bound. In another aspect, the present invention is directed towards the druggable region to which a hexane may bind in the subject structure. In another aspect, the present invention is directed toward the druggable regions along the interdimer interface.

EXAMPLE 16 Annotations

The functional annotation is arrived at by comparing the amino acid sequence of the ORF against all available ORFs in the NCBI database using BLAST. The closest match is selected to provide the probable function of the polypeptide having the sequence of SEQ ID NO: 2. Results of this comparison are described above and set forth in Table 2 of FIGURE 7.

The COGs database (Tatusov RL, Koonin EV, Lipman DJ. Science 1997; 278 (5338) 631-37) classifies proteins encoded in twenty-one completed genomes on the basis of sequence similarity. Members of the same Cluster of Orthologous Group, ("COG"), are expected to have the same or similar domain architecture and the same or substantially similar biological activity. The database may be used to predict the function of uncharacterised proteins through their homology to characterized proteins. The COGs database may be searched from NCBI's website (http://www.ncbi.nlm.nih.gov/COG/) to determine functional annotation descriptions, such as "information storage and processing" (translation, ribosomal structure and biogenesis, transcription, DNA replication,

recombination and repair); "cellular processes" (cell division and chromosome partitioning, post-translational modification, protein turnover, chaperones, cell envelope biogenesis, outer membrane, cell motility and secretion, inorganic ion transport and metabolism, signal transduction mechanisms); or "metabolism" (energy production and conversion, carbohydrate transport and metabolism, amino acid transport and metabolism, nucleotide transport and metabolism, coenzyme metabolism, lipid metabolism). For certain polypeptides, there is no entry available. Results of this analysis are described above and set forth in Table 2 of FIGURE 7.

EXAMPLE 17 Essential Gene Analysis

SEQ ID NO: 2 is compared to a number of publicly available "essential genes" lists to determine whether that protein is encoded by an essential gene. An example of such a list is descended from a free release at the www.shigen.nig.ac.jp PEC (profiling of *E. coli* chromosome) site, http://www.shigen.nig.ac.jp/ecoli/pec/. The list is prepared as follows: a wildcard search for all genes in class "essential" yields the list of essential *E. coli* proteins encoded by essential genes, which number 230. These 230 hits are pruned by comparing against an NCBI *E. coli* genome. Only 216 of the 230 genes on the list are found in the NCBI genome. These 216 are termed the essential-216-ecoli list. The essential-216-ecoli list is used to garner "essential" genes lists for other microbial genomes by blasting. For instance, formatting the 216-ecoli as a BLAST database, then BLASTing a genome (e.g. *S. aureus*) against it, elucidates all *S. aureus* genes with significant homology to a gene in the 216-essential list. SEQ ID NO: 2 is compared against the appropriate list and a match with a score of e^{-25} or better is considered an essential gene according to that list. In addition to the list described above, other lists of essential genes are publicly available or may be determined by methods disclosed publicly, and such lists and methods are considered in deciding whether a gene is essential. See, for example, Thanassi et al., Nucleic Acids Res 2002 Jul 15;30(14):3152-62; Forsyth et al., Mol Microbiol 2002 Mar;43(6):1387-400; Ji et al., Science 2001 Sep 21;293(5538):2266-9; Sassetti et al., Proc Natl Acad Sci U S A 2001 Oct 23;98(22):12712-7; Reich et al., J Bacteriol 1999 Aug;181(16):4961-8; Akerley et al., Proc Natl Acad Sci U S A 2002 Jan 22;99(2):966-71). Also, other methods are known in the art for determing whether a gene is essential, such as that disclosed in U.S. Patent Application No. 10/202,442 (filed July 24, 2002). The conclusion as to whether the gene

encoding the amino acid sequence set forth in SEQ ID NO: 2 is essential is set forth in Table 2 of FIGURE 7.

EXAMPLE 18 PDB Analysis

SEQ ID NO: 2 is compared against the amino acid sequences in a database of proteins whose structures have been solved and released to the PDB (protein data bank). The identity/information about the top PDB homolog (most similar "hit", if any; a PDB entry is only considered a hit if the score is e^{-4} or better) is annotated, and the percent similarity and identity between SEQ ID NO: 2 and the closest hit is calculated, with both being indicated in Table 2 of FIGURE 7.

EXAMPLE 19 Virtual Genome Analysis

VGDB or VG is a queryable collection of microbial genome databases annotated with biophysical and protein information. The organisms present in VG include:

File	GRAM	Species	Source	Genome file date
ecoli.faa	G-	*Escherichia coli*	NCBI	November 18 1998
hpyl.faa	G-	*Helicobacter pylori*	NCBI	April 19 1999
paer.faa	G-	*Pseudomonas aeruginosa*	NCBI	September 22 2000
ctra.faa	G-	*Chlamydia trachomatis*	NCBI	December 22 1999
hinf.faa	G-	*Haemophilus influenzae*	NCBI	November 26 1999
nmen.faa	G-	*Neisseria meningitidis*	NCBI	December 28 2000
rpxx.faa	G-	*Rickettsia prowazekii*	NCBI	December 22 1999
bbur.faa	G-	*Borrelia burgdorferi*	NCBI	November 11 1998
bsub.faa	G+	*Bacillus subtilis*	NCBI	December 1 1999
staph.faa	G+	*Staphylococcus aureus*	TIGR	March 8 2001
spne.faa	G+	*Streptococcus pneumoniae*	TIGR	February 22 2001
mgen.faa	G+	*Mycoplasma genitalium*	NCBI	November 23 1999
efae.faa	G+	*Enterococcus faecalis*	TIGR	March 8 2001

The VGDB comprises 13 microbial genomes, annotated with biophysical information (pI, MW, etc), and a wealth of other information. These 13 organism genomes are stored in a single flatfile (the VGDB) against which PSI-blast queries can be done.

SEQ ID NO: 2 is queried against the VGDB to determine whether this sequence is found, conserved, in many microbial genomes. There are certain criteria that must be met for a positive hit to be returned (beyond the criteria inherent in a basic PSI-blast).

When an ORF is queried it may have a maximum of 13 VG-organism hits. A hit is classified as such as long as it matches the following criteria: Minimum Length (as percentage of query length): 75 *(Ensure hit protein is at least 75% as long as query)*; Maximum Length (as percentage of query length): 125 *(Ensure hit protein is no more than 125% as long as query)*; eVal:-10 *(Ensure hit has an e-Value of e-10 or better)*; Id%:>:25 *(Ensure hit protein has at least 25% identity to query)*. The e-Value is a standard parameter of BLAST sequence comparisons, and represents a measure of the similarity between two sequences based on the likelihood that any similarities between the two sequences could have occurred by random chance alone. The lower the e-Value, the less likely that the similarities could have occurred randomly and, generally, the more similar the two sequences are.

The organisms having an orthologue of the polypeptide having SEQ ID NO: 2 are listed in Table 2, shown in FIGURE 7.

EXAMPLE 20 Epitopic Regions

The three most likely epitopic regions of a polypeptide having SEQ ID NO: 2 are predicted using the semi-empirical method of Kolaskar and Tongaonkar (FEBS Letters 1990 v276 172-174), the software package called Protean (DNASTAR), or MacVectors's Protein analysis tools (Accerlyrs). The antigenic propensity of each amino acid is calculated by the ratio between frequency of occurrence of amino acids in 169 antigenic determinants experimentally determined and the calculated frequency of occurrence of amino acids at the surface of protein. The results of these bioinformatics analyses are presented in Table 2, shown in FIGURE 7.

EQUIVALENTS

The present invention provides among other things novel proteins, protein structures and protein-protein interactions. While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations

of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. To the extent that any U.S. Provisional Patent Applications to which this patent application claims priority incorporate by reference another U.S. Provisional Patent Application, such other U.S. Provisional Patent Application is not incorporated by reference herein unless this patent application expressly incorporates by reference, or claims priorty to, such other U.S. Provisional Patent Application.

Also incorporated by reference in their entirety are any polynucleotide and polypeptide sequences which reference an accession number correlating to an entry in a public database, such as those maintained by The Institute for Genomic Research (TIGR) (www.tigr.org) and/or the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov).

Also incorporated by reference are the following: WO 00/45168, WO 00/79238, WO 00/77712, EP 1047108, EP 1047107, WO 00/72004, WO 00/73787, WO00/67017, WO 00/48004, WO 01/48209, WO 00/45168, WO 00/45164, U.S.S.N. 09/720272; PCT/CA99/00640; U.S. Patent Application Nos: 10/097125 (filed March 12, 2002); 10/097193 (filed March 12, 2002); 10/202442 (filed July 24, 2002); 10/097194 (filed March 12, 2002); 09/671817 (filed September 17, 2000); 09/965654 (filed September 27, 2001); 09/727812 (filed November 30, 2000); 60/370667 (filed April 8, 2002); a utility patent application entited "Methods and Appartuses for Purification" (filed September 18, 2002); U.S. Patent Numbers 6451591; 6254833; 6232114; 6229603; 6221612; 6214563; 6200762; 6171780; 6143492; 6124128; 6107477; D428157; 6063338; 6004808; 5985214; 5981200; 5928888; 5910287; 6248550; 6232114; 6229603; 6221612; 6214563; 6200762; 6197928; 6180411; 6171780; 6150176; 6140132; 6124128; 6107066; 6270988; 6077707; 6066476; 6063338; 6054321; 6054271; 6046925; 6031094; 6008378; 5998204; 5981200; 5955604; 5955453; 5948906; 5932474; 5925558; 5912137; 5910287; 5866548; 6214602; 5834436; 5777079; 5741657; 5693521; 5661035; 5625048; 5602258; 5552555; 5439797;

5374710; 5296703; 5283433; 5141627; 5134232; 5049673; 4806604; 4689432; 4603209; 6217873; 6174530; 6168784; 6271037; 6228654; 6184344; 6040133; 5910437; 5891993; 5854389; 5792664; 6248558; 6341256; 5854922; and 5866343; and Albin, R. and P. M. Silverman (1984). Mol Gen Genet 197(2): 261-71; Aqvist, J. and M. Fothergill (1996). J Biol Chem 271(17): 10010-6; Burton, P. M. and S. G. Waley (1968). Biochim Biophys Acta 151(3): 714-5; Campbell, I. D., R. B. Jones, et al. (1979). Biochem J 179(3): 607-21; Delboni, L. F., S. C. Mande, et al. (1995). Protein Sci 4(12): 2594-604; Fenn, R. H. and G. E. Marshall (1972). Biochem J 130(1): 1-10; Garza-Ramos, G., N. Cabrera, et al. (1998). Eur J Biochem 253(3): 684-91; Gibson, D. R., R. W. Gracy, et al. (1980). J Biol Chem 255(19): 9369-74; Gomez-Puyou, A., E. Saavedra-Lira, et al. (1995). Chem Biol 2(12): 847-55; Hartman, F. C. (1968). Biochem Biophys Res Commun 33(6): 888-94; Hartman, F. C. (1970). Biochemistry 9(8): 1783-91; Hartman, F. C. (1970). Biochemistry 9(8): 1776-82; Hartman, F. C. (1971). Biochemistry 10(1): 146-54; Hartman, F. C., G. M. LaMuraglia, et al. (1975). Biochemistry 14(24): 5274-9; Hartman, F. C. and I. C. Norton (1977). Methods Enzymol 47: 479-98; Heinz, D. W., M. Ryan, et al. (1995). Embo J 14(16): 3855-63; Johnson, L. N. and R. Wolfenden (1970). J Mol Biol 47(1): 93-100; Jones, R. B. and S. G. Waley (1979). Biochem J 179(3): 623-30; Jones, A. R. and S. J. Cooney (1987). Biochem Biophys Res Commun 145(3): 1054-8; Jones, A. R. and L. M. Porter (1995). Reprod Fertil Dev 7(5): 1089-94; Joubert, F., A. W. Neitz, et al. (2001). Proteins 45(2): 136-43; Krietsch, W. K., P. G. Pentchev, et al. (1970). Eur J Biochem 14(2): 289-300; Kursula, I., S. Partanen, et al. (2001). Eur J Biochem 268(19): 5189-96; Lolis, E. and G. A. Petsko (1990) Biochemistry 29(28): 6619-25; Marks, G. T., T. K. Harris, et al. (2001). Biochemistry 40(23): 6805-18; Mendz, G. L., S. L. Hazell, et al. (1994). Arch Biochem Biophys 312(2): 349-56; Nader, W., A. Betz, et al. (1979). Biochim Biophys Acta 571(2): 177-85; Niitsu, Y., O. Hori, et al. (1999). Brain Res Mol Brain Res 74(1-2): 26-34; Noble, M. E., C. L. Verlinde, et al. (1991). J Med Chem 34(9): 2709-18; Noble, M. E., R. K. Wierenga, et al. (1991). Proteins 10(1): 50-69; Norton, I. L. and F. C. Hartman (1972). Biochemistry 11(24): 4435-41; O'Connell, E. L. and I. A. Rose (1977). Methods Enzymol 46: 381-8; Ostoa-Saloma, P., G. Garza-Ramos, et al. (1997). Eur J Biochem 244(3): 700-5; Rose, I. A. and E. L. O'Connell (1969). J Biol Chem 244(23): 6548-50; Saadat, D. and D. H. Harrison (2000). Biochemistry 39(11): 2950-60; Thomas, M. K. and T. G. Spring (1976). Biochem J 153(3): 741-4; Verlinde, C. L. M. J.; Rudenko, G.; Hol, W. G. J. J. Comput. Aided Mol. Design 6, 131 (1992); Gao, X.-G., et al. (1999) Proc. Natl. Acad. Sci. USA 96, 10062;

Maldonado, E., et al. (1998) J. Mol. Biol. 283, 193 ; Raines, R. T., et al. (1986) Biochemistry 25, 7142-7154; Joseph-McCarthy, D. D., et al. (1994) Biochem. 33, 2815; Otwinowski, Z. and W. Minor (1997). Methods in Enzymology, vol. 276: Macromolecular Crystallography (Part A), p. 307-326, C. W. Carter, Jr. and R. M. Sweet, Eds., Academic Press; Brunger, A. T. et al. (1998) Acta Crystallogr. D. Biol. Crystallogr. 54, 905-921; Noble, M. E. M., et al, J. A. (1993) Acta Crystallogr D Biol Crystallogr 49 403; Velanker, S. S., S. S. Ray, et al. (1997). Structure 5(6): 751-61; Verlinde, C. L., C. J. Witmans, et al. (1992). Protein Sci 1(12): 1578-84; Verlinde, C. L., G. Rudenko, et al. (1992). J Comput Aided Mol Des 6(2): 131-47; Verlinde, C. L., E. A. Merritt, et al. (1994). Protein Sci 3(10): 1670-86; E.Lolis, G.A.Petsko. Biochem. 29, 6619 (1990); Waley, S. G., J. C. Miller, et al. (1970) Nature 227(254): 1811 and Zubillaga, R. A., R. Perez-Montfort, et al. (1994). Arch Biochem Biophys 313(2): 328-36.

We claim:

CLAIMS

1. A composition comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and wherein the polypeptide of (a), (b) or (c) is at least about 90% pure in a sample of the composition.

2. The composition of claim 1, wherein the polypeptide is at least about 95% pure as determined by gel electrophoresis.

3. The composition of claim 1, wherein the polypeptide is purified to essential homogeneity.

4. The composition of claim 1, wherein at least about two-thirds of the polypeptide in the sample is soluble.

5. The composition of claim 1, wherein the polypeptide is fused to at least one heterologous polypeptide that increases the solubility or stability of the polypeptide.

6. The composition of claim 1, which further comprises a matrix suitable for mass spectrometry.

7. The composition of claim 6, wherein the matrix is a nicotinic acid derivative or a cinnamic acid derivative.

8. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and wherein the polypeptide of (a), (b) or (c) is labeled with a heavy atom.

9. The sample of claim 8, wherein the heavy atom is one of the following: cobalt, selenium, krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium.

10. The sample of claim 8, wherein the polypeptide is labeled with seleno-methionine.

11. The sample of claim 8, further comprising a cryo-protectant.

12. The sample of claim 11, wherein the cryo-protectant is one of the following: methyl pentanediol, isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil and a low-molecular-weight polyethylene glycol.

13. A crystallized, recombinant polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; wherein the polypeptide of (a), (b) or (c) is in crystal form.

14. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a co-factor, wherein the complex is in crystal form.

15. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a small organic molecule, wherein the complex is in crystal form.

16. The crystallized, recombinant polypeptide of claim 13, which diffracts x-rays to a resolution of about 3.5 Å or better.

17. The crystallized, recombinant polypeptide of claim 13, wherein the polypeptide comprises at least one heavy atom label.

18. The crystallized, recombinant polypeptide of claim 17, wherein the polypeptide is labeled with seleno-methionine.

19. A method for designing a modulator for the prevention or treatment of *P. aeruginosa* related disease or disorder, comprising:

(a) providing a three-dimensional structure for a crystallized, recombinant polypeptide of claim 13;

(b) identifying a potential modulator for the prevention or treatment of *P. aeruginosa* related disease or disorder by reference to the three-dimensional structure;

(c) contacting a polypeptide of the composition of claim 1 or *P. aeruginosa* with the potential modulator; and

(d) assaying the activity of the polypeptide or determining the viability of *P. aeruginosa* after contact with the modulator, wherein a change in the activity of the polypeptide or the viability of *P. aeruginosa* indicates that the modulator may be useful for prevention or treatment of a *P. aeruginosa* related disease or disorder.

20. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and wherein the polypeptide of (a), (b) or (c) is enriched in at least one NMR isotope.

21. The sample of claim 20, wherein the NMR isotope is one of the following: hydrogen-1 (^{1}H), hydrogen-2 (^{2}H), hydrogen-3 (^{3}H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F).

22. The sample of claim 20, further comprising a deuterium lock solvent.

23. The sample of claim 22, wherein the deuterium lock solvent is one of the following: acetone (CD_3COCD_3), chloroform ($CDCl_3$), dichloro methane (CD_2Cl_2), methylnitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether ($(CD_3CD_2)_2O$), dimethylether ($(CD_3)_2O$), N,N-dimethylformamide ($(CD_3)_2NCDO$), dimethyl sulfoxide (CD_3SOCD_3), ethanol (CD_3CD_2OD), methanol (CD_3OD), tetrahydrofuran (C_4D_8O), toluene ($C_6D_5CD_3$), pyridine (C_5D_5N) and cyclohexane (C_6H_{12}).

24. The sample of claim 20, which is contained within an NMR tube.

25. A method for identifying small molecules that bind to a polypeptide of the composition of claim 1, comprising:

(a) generating a first NMR spectrum of an isotopically labeled polypeptide of the composition of claim 1;

(b) exposing the polypeptide to one or more small molecules;

(c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more small molecules; and

(d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more small molecules that have bound to the polypeptide.

26. A host cell comprising a nucleic acid encoding a polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; wherein a culture of the host cell produces at least about 1 mg of the polypeptide per liter of culture and the polypeptide is at least about one-third soluble as measured by gel electrophoresis.

27. An isolated, recombinant polypeptide, comprising: (a) an amino acid sequence having at least about 90% identity with the amino acid sequence set forth in SEQ ID NO: 4; or (b) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and wherein the polypeptide comprises one or more of the following amino acid residues at the specified position of the polypeptide: N at position 152, and S at position 233.

28. A method for obtaining structural information of a crystallized polypeptide, the method comprising:

(a) crystallizing a recombinant polypeptide, wherein the polypeptide comprises: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide

that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and wherein the crystallized polypeptide is capable of diffracting X-rays to a resolution of 3.5 Å or better; and

(b) analyzing the crystallized polypeptide by X-ray diffraction to determine the three-dimensional structure of at least a portion of the crystallized polypeptide.

29. The method of claim 28, wherein the three-dimensional structure of the portion of the crystallized polypeptide is determined to a resolution of 3.5 Å or better.

30. A method for identifying a druggable region of a polypeptide, the method comprising:

(a) obtaining crystals of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*, such that the three dimensional structure of the crystallized polypeptide may be determined to a resolution of 3.5 Å or better;

(b) determining the three dimensional structure of the crystallized polypeptide using X-ray diffraction; and

(c) identifying a druggable region of the crystallized polypeptide based on the three-dimensional structure of the crystallized polypeptide.

31. The method of claim 30, wherein the druggable region is an active site.

32. The method of claim 31, wherein the druggable region is on the surface of the polypeptide.

33. Crystalline triosephosphate isomerase from *P. aeruginosa* comprising a hexagonal crystal having unit cell dimensions of a = 77.349, c = 175.528 Å, and space group $P6_1$, the unit cell containing two molecules per asymmetric unit.

34. A crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3)

an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; wherein the crystal has a $P6_1$ space group.

35. A crystallized polypeptide comprising a structure of a polypeptide that is defined by a substantial portion of the atomic coordinates set forth in FIGURE 9.

36. A method for determining the crystal structure of a homolog of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a first crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*;

(b) obtaining crystals of a second polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, such that the three dimensional structure of the second crystallized polypeptide may be determined to a resolution of 3.5 Å or better; and

(c) determining the three dimensional structure of the second crystallized polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a).

37. The method of claim 36, wherein the atomic coordinates for the second crystallized polypeptide have a root mean square deviation from the backbone atoms of the first polypeptide of not more than 1.5 Å for all backbone atoms shared in common with the first polypeptide and the second polypeptide.

38. A method for homology modeling a homolog of triosephosphate isomerase from *P. aeruginosa*, comprising:

(a) aligning the amino acid sequence of a homolog of triosephosphate isomerase from *P. aeruginosa* with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and incorporating the sequence of the homolog of triosephosphate isomerase from

P. aeruginosa into a model of triosephosphate isomerase from *P. aeruginosa* derived from structure coordinates as listed in FIGURE 9 to yield a preliminary model of the homolog of triosephosphate isomerase from *P. aeruginosa*;

(b) subjecting the preliminary model to energy minimization to yield an energy minimized model;

(c) remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog of triosephosphate isomerase from *P. aeruginosa*.

39. A method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising:

(a) crystallizing the molecule or molecular complex;

(b) generating an x-ray diffraction pattern from the crystallized molecule or molecular complex;

(c) applying at least a portion of the structure coordinates set forth in FIGURE 9 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

40. A method for attempting to make a crystallized complex comprising a polypeptide and a modulator having a molecular weight of less than 5 kDa, the method comprising:

(a) crystallizing a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; such that crystals of the crystallized polypeptide will diffract x-rays to a resolution of 5 Å or better; and

(b) soaking the crystals in a solution comprising a potential modulator having a molecular weight of less than 5 kDa.

41. A method for incorporating a potential modulator in a crystal of a polypeptide, comprising placing a hexagonal crystal of triosephosphate isomerase from *P. aeruginosa*

having unit cell dimensions of a = 77.349, c = 175.528 Å and space group $P6_1$ in a solution comprising the potential modulator.

42. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprises structural coordinates as listed in FIGURE 9 for the backbone atoms of at least about six amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa.*

43. A scalable three-dimensional configuration of points, at least a portion of the points derived from some or all of the structure coordinates as listed in FIGURE 9 for a plurality of amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa.*

44. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 9 for the backbone atoms of at least about five amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa* are used to derive part or all of the portion of points.

45. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 9 for the backbone and optionally the side chain atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa* are used to derive part or all of the portion of points.

46. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 9 for the backbone atoms of at least about fifteen amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa* are used to derive part or all of the portion of points.

47. The scalable three-dimensional configuration of points of claim 43, wherein substantially all of the points are derived from structure coordinates as listed in FIGURE 9.

48. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 9 for one or more of the following groups of atoms from a druggable region of triosephosphate isomerase from *P. aeruginosa* are used to derive part or all of the portion of points:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*.

49. A scalable three-dimensional configuration of points, comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 9 for the backbone atoms of at least five amino acid residues, wherein the five amino acid residues are from a druggable region of triosephosphate isomerase from *P. aeruginosa*.

50. The scalable three-dimensional configuration of points of claim 49, wherein any point-to-point distance, calculated from the three dimensional coordinates as listed in FIGURE 9, between one of the backbone atoms for one of the five amino acid residues and another backbone atom of a different one of the five amino acid residues is not more than about 10 Å.

51. A scalable three-dimensional configuration of points comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 9 for one or more of the following groups of atoms from a druggable region of triosephosphate isomerase from *P. aeruginosa*:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*.

52. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise the identity and three-dimensional coordinates as listed in FIGURE 9 for one of the following groups of atoms from a druggable region of triosephosphate isomerase from *P. aeruginosa*:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*.

53. A scalable three-dimensional configuration of points, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 9 for the atoms of one or more of the following groups from a druggable region of triosephosphate isomerase from *P. aeruginosa*:

(i) the atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the atoms of Glu165 and His95;

(iii) the atoms of Glu165, His95, Asn10 and Lys12;

(iv) the atoms for all of Arg134, Thr139, and Glu185;

(v) the atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the atoms for all of Leu74, Ile101 and Leu102;

(vii) the atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the atoms of Cys43 and optionally Cys88 and the atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*;

wherein up to one amino acid residue in each of the groups (i) to (ix) may have a conservative substitution thereof.

54. A scalable three-dimensional configuration of points derived from a druggable region of a polypeptide, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 9 for the backbone

atoms of at least ten amino acid residues that participate in the intersubunit contacts of triosephosphate isomerase from *P. aeruginosa.*

55. The scalable three-dimensional configuration of points of claim 54, wherein one of the ten amino acid residues is Cys43.

56. A computer-assisted method for identifying an inhibitor of the activity of triosephosphate isomerase from *P. aeruginosa*, comprising:

(a) supplying a computer modeling application with a set of structure coordinates as listed in FIGURE 9 for atoms from one or more of the following groups so as to define part or all of a molecule or complex:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*;

(b) supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

(c) determining whether the chemical entity is expected to bind to or interfere with the molecule or complex.

57. The method of claim 56, wherein determining whether the chemical entity is expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

58. The method of claim 56, further comprising screening a library of chemical entities.

59. A computer-assisted method for designing an inhibitor of triosephosphate isomerase activity comprising:

(a) supplying a computer modeling application with a set of structure coordinates having a root mean square deviation of less than about 1.5 Å from the structure coordinates as listed in FIGURE 9 for atoms from one or more of the following groups so as to define part or all of a molecule or complex:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*;

(b) supplying the computer modeling application with a set of structure coordinates for a chemical entity;

(c) evaluating the potential binding interactions between the chemical entity and the molecule or complex;

(d) structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

(e) determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of triosephosphate isomerase activity.

60. The method of claim 59, wherein determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and the molecule or complex, followed by computationally analyzing the results of the fitting operation to evaluate the association between the chemical entity and the molecule or complex.

61. The method of claim 59, wherein the set of structure coordinates for the chemical entity is obtained from a chemical library.

62. A computer-assisted method for designing an inhibitor of triosephosphate isomerase activity *de novo* comprising:

(a) supplying a computer modeling application with a set of three-dimensional coordinates derived from the structure coordinates as listed in FIGURE 9 for atoms from one or more of the following groups so as to define part or all of a molecule or complex:

(i) the backbone atoms of at least a majority of Pro166, Val167, Trp168, Ala169, Ile170, Gly171, Thr172, Gly173, Leu174, Thr175 and Ala176;

(ii) the backbone atoms of Glu165 and the backbone atoms and three or more of the side chain atoms of His95;

(iii) the backbone atoms of Glu165, His95, Asn10 and Lys12;

(iv) the backbone atoms for all of Arg134, Thr139, and Glu185;

(v) the backbone atoms for at least four of Ala67, Leu102, Gly103, Val108, Lys112, Ile101, and Leu102;

(vi) the backbone atoms for all of Leu74, Ile101 and Leu102;

(vii) the backbone atoms of at least about ten amino acid residues from a druggable region of triosephosphate isomerase from *P. aeruginosa*;

(viii) the backbone atoms of at least ten of the amino acid residues identified in Table 4 of FIGURE 17; or

(ix) the backbone and side chain atoms of Cys43 and optionally Cys88 and the backbone atoms of at least three other amino acid residues that may be involved in the intersubunit interaction of a dimer of triosephosphate isomerase from *P. aeruginosa*;

(b) computationally building a chemical entity represented by a set of structure coordinates; and

(c) determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of triosephosphate isomerase activity.

63. The method of claim 62, wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

64. The method of any of claims 56, 59 or 62, further comprising supplying or synthesizing the potential inhibitor, then assaying the potential inhibitor to determine whether it inhibits triosephosphate isomerase activity.

65. A method for identifying a potential modulator for the prevention or treatment of a *P. aeruginosa* related disease or disorder, the method comprising:

(a) providing the three dimensional structure of a crystallized polypeptide comprising: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*;

(b) obtaining a potential modulator for the prevention or treatment of *P. aeruginosa* related disease or disorder based on the three dimensional structure of the crystallized polypeptide;

(c) contacting the potential modulator with a second polypeptide comprising: (i) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (ii) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (iii) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; which second polypeptide may optionally be the same as the crystallized polypeptide; and

(d) assaying the activity of the second polypeptide, wherein a change in the activity of the second polypeptide indicates that the compound may be useful for prevention or treatment of a *P. aeruginosa* related disease or disorder.

66. A method for designing a candidate modulator for screening for inhibitors of a polypeptide, the method comprising:

(a) providing the three dimensional structure of a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*; and

(b) designing a candidate modulator based on the three dimensional structure of the druggable region of the polypeptide.

67. A method for identifying a potential modulator of a polypeptide from a database, the method comprising:

(a) providing the three-dimensional coordinates for a plurality of the amino acids of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence

encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*;

(b) identifying a druggable region of the polypeptide; and

(c) selecting from a database at least one potential modulator comprising three dimensional coordinates which indicate that the modulator may bind or interfere with the druggable region.

68. The method of claim 67, wherein the modulator is a small molecule.

69. A method for preparing a potential modulator of a druggable region contained in a polypeptide, the method comprising:

(a) using the atomic coordinates for the backbone atoms of at least about six amino acid residues from a polypeptide of SEQ ID NO: 4, with a ± a root mean square deviation from the backbone atoms of the amino acid residues of not more than 1.5 Å, to generate one or more three-dimensional structures of a molecule comprising a druggable region from the polypeptide;

(b) employing one or more of the three dimensional structures of the molecule to design or select a potential modulator of the druggable region; and

(c) synthesizing or obtaining the modulator.

70. An apparatus for determining whether a compound is a potential modulator of a polypeptide, the apparatus comprising:

(a) a memory that comprises:

(i) the three dimensional coordinates and identities of at least about fifteen atoms from a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of triosephosphate isomerase from *P. aeruginosa*;

(ii) executable instructions; and

(b) a processor that is capable of executing instructions to:

(i) receive three-dimensional structural information for a candidate modulator;

(ii) determine if the three-dimensional structure of the candidate modulator is complementary to the three dimensional coordinates of the atoms from the druggable region; and

(iii) output the results of the determination.

71. A method for making an inhibitor of triosephosphate isomerase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an inhibitor of triosephosphate isomerase activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex comprising at least a portion of at least one druggable region from triosephosphate isomerase from *P. aeruginosa*; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind or to interfere with the molecule or complex at a druggable region, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of triosephosphate isomerase activity.

72. A computer readable storage medium comprising digitally encoded data, wherein the data comprises structural coordinates for a druggable region that is structurally homologous to the structure coordinates as listed in FIGURE 9 for a druggable region of triosephosphate isomerase from *P. aeruginosa*.

73. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise a majority of the three-dimensional structure coordinates as listed in FIGURE 9.

74. The computer readable storage medium of claim 73, further comprising the identity of the atoms for the majority of the three-dimensional structure coordinates as listed in FIGURE 9.

75. The computer readable storage medium of claim 73, wherein the data comprise substantially all of the three-dimensional structure coordinates as listed in FIGURE 9.

FIGURE 1

SEQ ID NO: 1

ATGCGTCGACCCTTGGTGGCCGGTAACTGGAAAATGCACGGTACGCATT
CCAGTGTGGCCGAGTTGATCAAAGGCTTGCGTCAGCTGGCGTTGCCGAGCGGA
GTCGATGTGGCTGTGATGCCGCCTTGCTTGTTCATCAGCCAGGTCATCCAGGGC
CTGGCCGGCAAGGCGATCGATGTAGGTGCGCAGAACAGCGCCGTCGAGCCGAT
GCAAGGCGCGCTGACCGGTGAGACTGCTCCCAGTCAGTTGGCGGATGTCGGTT
GTAGCATGGTCCTTGTGGGCCACTCGGAGCGTCGCCTGATTCTCGGCGAGAGTG
ACGAGGTTGTGAGTCGCAAGTTTGCCGCGGCTCAGTCGTGCGGCCTGGTGCCGG
TGCTGTGTGTCGGGGAGACCCGGGCGGAGCGCGAGGCGGGCAAGACGCTGGA
GGTTGTCGCAAGGCAGCTGGGAAGCGTGATCGACGAGTTGGGTGTTGGAGCTT
TTGCTCGCGCAGTCGTGGCTTACGAGCCGGTCTGGGCGATCGGGACCGGGTTGA
CCGCGTCCCCCGCGCAAGCCCAGGAAGTGCACGCGGCGATCCGCGCGCAACTG
GCAGCGGAAAATGCCGAGGTCGCAAAAGGTGTGCGACTCCTTTACGGCGGCAG
TGTAAAGGCGGCAAGTGCAGCCGAGTTGTTCGGCATGCCGGATATCGATGGGG
GGCTGGTAGGTGGAGCCTCCCTCAATGCGGATGAGTTCGGCGCGATCTGTCGTG
CCGCGGGAAGCTGA

FIGURE 2

SEQ ID NO: 2

MRRPLVAGNWKMHGTHSSVAELIKGLRQLALPSGVDVAVMPPCLFISQVIQ
GLAGKAIDVGAQNSAVEPMQGALTGETAPSQLADVGCSMVLVGHSERRLILGESD
EVVSRKFAAAQSCGLVPVLCVGETRAEREAGKTLEVVARQLGSVIDELGVGAFAR
AVVAYEPVWAIGTGLTASPAQAQEVHAAIRAQLAAENAEVAKGVRLLYGGSVKA
ASAAELFGMPDIDGGLVGGASLNADEFGAICRAAGS

FIGURE 3

SEQ ID NO: 3

ATGCGTCGACCCTTGGTGGCCGGTAACTGGAAAATGCACGGTACGCATT
CCAGTGTGGCCGAGTTGATCAAAGGCTTGCGTCAGCTGGCGTTGCCGAGCGGA
GTCGATGTAGCTGTGATGCCGCCTTGCTTGTTCATCAGCCAGGTCATCCAGGGC
CTGGCCGGCAAGGCGATCGATGTAGGTGCGCAGAACAGCGCCGTCGAGCCGAT
GCAAGGCGCGCTGACCGGTGAGACTGCTCCCAGTCAGTTGGCGGATGTCGGTT
GTAGCATGGTCCTCGTGGGCCACTCGGAGCGTCGCCTGATTCTCGGCGAGAGTG
ACGAGGTTGTGAGTCGCAAGTTTGCCGCGGCTCAGTCGTGCGGCCTGGTGCCGG
TGCTGTGTGTCGGGGAGACCCGGGCGGAGCGCGAGGCGGGCAAGACGCTGGA
GGTTGTCGCAAGGCAGCTGGGAAGCGTGATCAACGAGTTGGGTGTTGGAGCTT
TTGCTCGCGCAGTCGTGGCTTACGAGCCGGTCTGGGCGATCGGGACCGGGTTGA
CCGCGTCCCCCGCGCAAGCCCAGGAAGTGCACGCGGCGATCCGCGCGCAACTG
GCAGCGGAAAATGCCGAGGTCGCAAAAGGTGTGCGACTCCTTTACGGCGGCAG
TGTAAAGGCGGCAAGTGCAGCCGAGTTGTTCGGCATGCCGGATATCGATGGGG
GGCTGGTAAGTGGAGCCTCCCTCAATGCGGATGAGTTCGGCGCGATCTGTCGTG
CCGCGGGAAGCTGA

FIGURE 4

SEQ ID NO: 4

MRRPLVAGNWKMHGTHSSVAELIKGLRQLALPSGVDVAVMPPCLFISQVIQ
GLAGKAIDVGAQNSAVEPMQGALTGETAPSQLADVGCSMVLVGHSERRLILGESD
EVVSRKFAAAQSCGLVPVLCVGETRAEREAGKTLEVVARQLGSVINELGVGAFAR
AVVAYEPVWAIGTGLTASPAQAQEVHAAIRAQLAAENAEVAKGVRLLYGGSVKA
ASAAELFGMPDIDGGLVSGASLNADEFGAICRAAGS

FIGURE 5

SEQ ID NO; 5

Forward PCR Primer

GCGGCGGCATTAATATGAAAAATTGTGTCATCGTCAG

SEQ ID NO: 6

Reverse PCR Primer

GCGCGGATCCTTATTAATTCAACCGTTCAATCACC

FIGURE 6

TABLE 1: Amino Acid and Nucleic Acid Properties

Melting temperature (°C) of SEQ ID NO: 5 (forward PCR primer)	62
Restriction enzyme for SEQ ID NO: 5 (forward PCR primer)	AseI
Melting temperature (°C) of SEQ ID NO: 6 (reverse PCR primer)	60
Restriction enzyme for SEQ ID NO: 6 (reverse PCR primer)	BamHI
Number of nucleic acid residues in SEQ ID NO: 1	756
Number of amino acid residues in SEQ ID NO: 2	251
Number of different nucleic acid residues between SEQ ID NO: 1 and SEQ ID NO: 3	4
Number of different amino acid residues between SEQ ID NO: 2 and SEQ ID NO: 4	2
Calculated Molecular weight of SEQ ID NO: 2 polypeptide (kDa)	27.9
Calculated pI of SEQ ID NO: 2 polypeptide	5.2
Solubility of SEQ ID NO: 4 polypeptide, determined as described in EXAMPLE 2 (with the His tag at the N-terminus)	Approaching 100%
Amount of purified polypeptide having SEQ ID NO: 4, prepared and purified as described in EXAMPLE 7 (mg/L of culture)	49.3
Amount of purified selmet labeled polypeptide having SEQ ID NO: 4, prepared and purified as described in EXAMPLE 7 (mg/L of culture)	123.2
Amount of purified polypeptide having SEQ ID NO: 4 soluble in buffer, as described in EXAMPLE 7 (mg/ml of buffer)	45.8
Amount of purified selmet labeled polypeptide having SEQ ID NO: 4 soluble in buffer, as described in EXAMPLE 7 (mg/ml of buffer)	91.6

FIGURE 7

TABLE 2: Bioinformatic Analyses

Protein annotation and gene designation, if any	triosephosphate isomerase, *tpiA*
COG Category	carbohydrate transport and metabolism
COG ID Number	COG0149
Is SEQ ID NO: 2 classified as an essential gene?	yes
Most closely related protein from PDB	Triosephosphate Isomerase, (1tre_B)
Source organism for closest PDB protein	*E. coli*
% Identity between SEQ ID NO: 2 and the closest protein from PDB	52
% Positives between SEQ ID NO: 2 and the closest protein from PDB	67
Number of Protein Hits in the VGDB	12
Number of Microorganisms having VGDB Hits	12
Microorganisms having VGDB Hits[1]	[saur][paer][efae][bsub][spne][ctra] [ecoli][bbur][hinf][nmen][mgen][hpyl]
First predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.304,105->129, SDEVVSRKFAAAQSCGLVPVLCVGE (SEQ ID NO: 10)
Second predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.188,16->61, HSSVAELIKGLRQLALPSGVDVA VMPPCLFISQVIQGLAGKAIDVG (SEQ ID NO: 11)
Third predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.184,139->175, TLEVVARQLGSVIDELGVG AFARAVVAYEPVWAIGTG (SEQ ID NO: 12)

[1]Organisms are abbreviated as follows: ecoli = *Eschericia coli*; hpyl = *Helicobacter pylori*; paer = *Pseudomonas aeruginosa*; ctra = *Chlaydia trachomatis*; hinf = *Haemophilus influenzae*; nmen = *Neisseria meningitidis*; rpxx = *Rickettsia prowazekii*; bbur = *Borrelia burgdorferi*; bsub = *Bacillus subtilis*; staph = *Staphylococcus aureus*; spne = *Streptococcus pneumoniae*; mgen = *Mycoplasma genitalium*; efae = *Enterococcus faecalis*.

FIGURE 8

TABLE 3: X-ray Structure Data

Wavelength (Å)	0.9796
Resolution (Å)	15 – 2.2
Total Data	202,194
Unique Data	28,770
Redundancy	7.5
Overall Completeness*	95.9
Completeness (last shell)*	90.3
R_{merge} (overall)[a]	8.8
R_{merge} (last shell)[a]	15.4
$\langle I/\sigma(I)\rangle$	14.4

[a] $R_{merge} = \Sigma_{unique\ reflections} (\Sigma^{N}_{i=1}|I_i - \bar{I}|) / \Sigma_{unique\ reflections} (\Sigma^{N}_{i=1} I_i)$

* last shell includes all reflections between 2.28 and 2.20 Å.

FIGURE 8 -2

TABLE 3: X-ray Structure Data Continued

Final Model parameters	Number of amino acid chains	2
	Number of protein atoms	3576
	Number of solvent molecules	194
	Resolution range (Å)	15 – 2.2
	R-factor[b]	20.65
	R_{free}	25.03
	Average main chain / side chain B-factor (Å^2)	29.5
	Average solvent B-factor (Å^2)	35.4
RMS deviation from ideal geometry	Covalent bond lengths (Å)	0.010
	Bond angles (°)	1.288
	Improper angles (°)	0.842
	Dihedral angles (°)	22.587

[b]R-factor – $\Sigma_{hkl}||F_{obs}| - |F_{calc}||/\Sigma_{hkl}|F_{obs}|$

[c]R_{free} is a cross-validation residual calculated using 5% of the native data which were chosen randomly and excluded from the refinement.

FIGURE 9 - 1

ATOM	1	CB	MET	A	1	69.824	37.159	19.844	1.00	47.93	A	C
ATOM	2	CG	MET	A	1	70.963	36.609	20.697	1.00	51.83	A	C
ATOM	3	SD	MET	A	1	71.783	35.169	19.890	1.00	56.56	A	S
ATOM	4	CE	MET	A	1	73.200	36.024	18.993	1.00	54.75	A	C
ATOM	5	C	MET	A	1	69.421	35.932	17.696	1.00	42.10	A	C
ATOM	6	O	MET	A	1	68.625	36.084	16.759	1.00	43.43	A	O
ATOM	7	N	MET	A	1	69.697	38.417	17.710	1.00	45.33	A	N
ATOM	8	CA	MET	A	1	70.126	37.134	18.339	1.00	44.82	A	C
ATOM	9	N	ARG	A	2	69.734	34.738	18.186	1.00	37.50	A	N
ATOM	10	CA	ARG	A	2	69.122	33.518	17.688	1.00	33.20	A	C
ATOM	11	CB	ARG	A	2	70.096	32.342	17.808	1.00	31.53	A	C
ATOM	12	CG	ARG	A	2	71.365	32.478	16.972	1.00	30.51	A	C
ATOM	13	CD	ARG	A	2	72.265	31.262	17.156	1.00	25.81	A	C
ATOM	14	NE	ARG	A	2	72.686	31.138	18.543	1.00	26.87	A	N
ATOM	15	CZ	ARG	A	2	73.835	31.596	19.022	1.00	25.34	A	C
ATOM	16	NH1	ARG	A	2	74.698	32.205	18.221	1.00	24.74	A	N
ATOM	17	NH2	ARG	A	2	74.105	31.467	20.312	1.00	26.16	A	N
ATOM	18	C	ARG	A	2	67.885	33.245	18.536	1.00	30.48	A	C
ATOM	19	O	ARG	A	2	67.973	33.155	19.757	1.00	29.01	A	O
ATOM	20	N	ARG	A	3	66.737	33.119	17.883	1.00	28.55	A	N
ATOM	21	CA	ARG	A	3	65.476	32.861	18.569	1.00	29.41	A	C
ATOM	22	CB	ARG	A	3	64.332	33.036	17.575	1.00	30.70	A	C
ATOM	23	CG	ARG	A	3	62.936	33.054	18.153	1.00	31.57	A	C
ATOM	24	CD	ARG	A	3	61.944	33.346	17.030	1.00	32.95	A	C
ATOM	25	NE	ARG	A	3	60.551	33.310	17.463	1.00	35.33	A	N
ATOM	26	CZ	ARG	A	3	59.970	34.225	18.232	1.00	34.99	A	C
ATOM	27	NH1	ARG	A	3	60.664	35.269	18.664	1.00	35.09	A	N
ATOM	28	NH2	ARG	A	3	58.688	34.092	18.569	1.00	35.17	A	N
ATOM	29	C	ARG	A	3	65.490	31.438	19.131	1.00	28.70	A	C
ATOM	30	O	ARG	A	3	65.745	30.485	18.404	1.00	28.41	A	O
ATOM	31	N	PRO	A	4	65.234	31.278	20.440	1.00	28.03	A	N
ATOM	32	CD	PRO	A	4	64.972	32.307	21.460	1.00	28.75	A	C
ATOM	33	CA	PRO	A	4	65.234	29.940	21.044	1.00	27.75	A	C
ATOM	34	CB	PRO	A	4	64.912	30.220	22.512	1.00	28.22	A	C
ATOM	35	CG	PRO	A	4	65.433	31.615	22.721	1.00	27.20	A	C
ATOM	36	C	PRO	A	4	64.212	29.004	20.405	1.00	26.99	A	C
ATOM	37	O	PRO	A	4	63.154	29.443	19.951	1.00	26.58	A	O
ATOM	38	N	LEU	A	5	64.533	27.716	20.359	1.00	25.17	A	N
ATOM	39	CA	LEU	A	5	63.618	26.735	19.785	1.00	24.71	A	C
ATOM	40	CB	LEU	A	5	64.077	26.325	18.383	1.00	23.58	A	C
ATOM	41	CG	LEU	A	5	63.416	25.058	17.832	1.00	25.11	A	C
ATOM	42	CD1	LEU	A	5	61.910	25.222	17.776	1.00	24.31	A	C
ATOM	43	CD2	LEU	A	5	63.970	24.756	16.467	1.00	25.01	A	C
ATOM	44	C	LEU	A	5	63.489	25.494	20.669	1.00	23.84	A	C
ATOM	45	O	LEU	A	5	64.484	24.919	21.099	1.00	22.31	A	O
ATOM	46	N	VAL	A	6	62.250	25.106	20.949	1.00	22.72	A	N
ATOM	47	CA	VAL	A	6	61.980	23.926	21.762	1.00	22.86	A	C
ATOM	48	CB	VAL	A	6	61.255	24.284	23.081	1.00	23.69	A	C
ATOM	49	CG1	VAL	A	6	60.942	23.015	23.855	1.00	24.56	A	C
ATOM	50	CG2	VAL	A	6	62.127	25.203	23.925	1.00	21.51	A	C
ATOM	51	C	VAL	A	6	61.114	22.971	20.951	1.00	22.51	A	C
ATOM	52	O	VAL	A	6	59.976	23.280	20.617	1.00	21.30	A	O
ATOM	53	N	ALA	A	7	61.681	21.815	20.623	1.00	22.04	A	N
ATOM	54	CA	ALA	A	7	60.986	20.812	19.835	1.00	21.29	A	C
ATOM	55	CB	ALA	A	7	61.755	20.532	18.547	1.00	21.56	A	C
ATOM	56	C	ALA	A	7	60.829	19.537	20.639	1.00	20.53	A	C
ATOM	57	O	ALA	A	7	61.757	19.085	21.302	1.00	22.14	A	O
ATOM	58	N	GLY	A	8	59.638	18.968	20.573	1.00	20.59	A	N
ATOM	59	CA	GLY	A	8	59.360	17.749	21.296	1.00	21.98	A	C
ATOM	60	C	GLY	A	8	59.268	16.542	20.387	1.00	21.22	A	C
ATOM	61	O	GLY	A	8	58.391	16.458	19.524	1.00	20.48	A	O
ATOM	62	N	ASN	A	9	60.195	15.612	20.582	1.00	20.52	A	N
ATOM	63	CA	ASN	A	9	60.238	14.371	19.818	1.00	20.62	A	C

ATOM	64	CB	ASN	A	9	61.688	13.905	19.664	1.00	21.79	A	C
ATOM	65	CG	ASN	A	9	61.814	12.604	18.898	1.00	22.57	A	C
ATOM	66	OD1	ASN	A	9	60.860	12.131	18.267	1.00	23.21	A	O
ATOM	67	ND2	ASN	A	9	63.007	12.021	18.938	1.00	20.11	A	N
ATOM	68	C	ASN	A	9	59.438	13.330	20.588	1.00	18.69	A	C
ATOM	69	O	ASN	A	9	59.893	12.804	21.599	1.00	18.72	A	O
ATOM	70	N	TRP	A	10	58.241	13.029	20.110	1.00	18.64	A	N
ATOM	71	CA	TRP	A	10	57.405	12.053	20.788	1.00	19.21	A	C
ATOM	72	CB	TRP	A	10	55.954	12.163	20.293	1.00	19.06	A	C
ATOM	73	CG	TRP	A	10	55.307	13.527	20.505	1.00	19.67	A	C
ATOM	74	CD2	TRP	A	10	53.979	13.916	20.131	1.00	19.14	A	C
ATOM	75	CE2	TRP	A	10	53.828	15.280	20.476	1.00	18.55	A	C
ATOM	76	CE3	TRP	A	10	52.901	13.246	19.537	1.00	20.95	A	C
ATOM	77	CD1	TRP	A	10	55.888	14.642	21.052	1.00	20.26	A	C
ATOM	78	NE1	TRP	A	10	55.006	15.695	21.035	1.00	18.74	A	N
ATOM	79	CZ2	TRP	A	10	52.644	15.987	20.244	1.00	18.26	A	C
ATOM	80	CZ3	TRP	A	10	51.721	13.949	19.307	1.00	22.89	A	C
ATOM	81	CH2	TRP	A	10	51.605	15.311	19.661	1.00	19.41	A	C
ATOM	82	C	TRP	A	10	57.923	10.633	20.576	1.00	19.01	A	C
ATOM	83	O	TRP	A	10	57.626	9.740	21.360	1.00	21.00	A	O
ATOM	84	N	LYS	A	11	58.716	10.429	19.529	1.00	19.99	A	N
ATOM	85	CA	LYS	A	11	59.234	9.100	19.209	1.00	19.88	A	C
ATOM	86	CB	LYS	A	11	60.081	8.556	20.372	1.00	19.61	A	C
ATOM	87	CG	LYS	A	11	61.346	9.372	20.621	1.00	21.85	A	C
ATOM	88	CD	LYS	A	11	62.309	8.706	21.606	1.00	19.55	A	C
ATOM	89	CE	LYS	A	11	63.491	9.615	21.902	1.00	21.46	A	C
ATOM	90	NZ	LYS	A	11	64.357	9.126	23.015	1.00	21.50	A	N
ATOM	91	C	LYS	A	11	58.079	8.136	18.864	1.00	19.77	A	C
ATOM	92	O	LYS	A	11	57.011	8.578	18.442	1.00	19.57	A	O
ATOM	93	N	MET	A	12	58.293	6.836	19.047	1.00	19.49	A	N
ATOM	94	CA	MET	A	12	57.289	5.817	18.717	1.00	20.75	A	C
ATOM	95	CB	MET	A	12	57.992	4.469	18.499	1.00	17.93	A	C
ATOM	96	CG	MET	A	12	57.198	3.393	17.765	1.00	17.92	A	C
ATOM	97	SD	MET	A	12	58.141	1.848	17.540	1.00	9.74	A	S
ATOM	98	CE	MET	A	12	59.243	2.316	16.753	1.00	14.06	A	C
ATOM	99	C	MET	A	12	56.283	5.702	19.857	1.00	21.78	A	C
ATOM	100	O	MET	A	12	56.234	4.686	20.542	1.00	21.20	A	O
ATOM	101	N	HIS	A	13	55.482	6.748	20.051	1.00	22.25	A	N
ATOM	102	CA	HIS	A	13	54.501	6.772	21.132	1.00	22.79	A	C
ATOM	103	CB	HIS	A	13	55.025	7.623	22.297	1.00	21.95	A	C
ATOM	104	CG	HIS	A	13	56.214	7.042	22.999	1.00	22.25	A	C
ATOM	105	CD2	HIS	A	13	57.533	7.343	22.918	1.00	20.66	A	C
ATOM	106	ND1	HIS	A	13	56.111	6.020	23.918	1.00	19.93	A	N
ATOM	107	CE1	HIS	A	13	57.313	5.718	24.374	1.00	22.47	A	C
ATOM	108	NE2	HIS	A	13	58.194	6.506	23.782	1.00	21.78	A	N
ATOM	109	C	HIS	A	13	53.152	7.329	20.703	1.00	22.90	A	C
ATOM	110	O	HIS	A	13	53.059	8.095	19.748	1.00	25.02	A	O
ATOM	111	N	GLY	A	14	52.107	6.930	21.420	1.00	23.25	A	N
ATOM	112	CA	GLY	A	14	50.779	7.431	21.139	1.00	22.85	A	C
ATOM	113	C	GLY	A	14	49.759	6.512	20.499	1.00	23.50	A	C
ATOM	114	O	GLY	A	14	50.102	5.608	19.745	1.00	23.98	A	O
ATOM	115	N	THR	A	15	48.494	6.761	20.838	1.00	24.90	A	N
ATOM	116	CA	THR	A	15	47.331	6.053	20.301	1.00	27.25	A	C
ATOM	117	CB	THR	A	15	46.601	5.216	21.364	1.00	27.45	A	C
ATOM	118	OG1	THR	A	15	46.225	6.067	22.457	1.00	28.53	A	O
ATOM	119	CG2	THR	A	15	47.503	4.098	21.883	1.00	27.74	A	C
ATOM	120	C	THR	A	15	46.420	7.206	19.906	1.00	28.74	A	C
ATOM	121	O	THR	A	15	46.759	8.364	20.143	1.00	26.29	A	O
ATOM	122	N	HIS	A	16	45.265	6.916	19.324	1.00	30.03	A	N
ATOM	123	CA	HIS	A	16	44.387	8.005	18.924	1.00	32.19	A	C
ATOM	124	CB	HIS	A	16	43.164	7.481	18.157	1.00	34.83	A	C
ATOM	125	CG	HIS	A	16	42.518	8.524	17.301	1.00	38.07	A	C
ATOM	126	CD2	HIS	A	16	41.488	9.370	17.549	1.00	38.27	A	C
ATOM	127	ND1	HIS	A	16	43.014	8.875	16.061	1.00	38.87	A	N
ATOM	128	CE1	HIS	A	16	42.318	9.895	15.586	1.00	39.88	A	C
ATOM	129	NE2	HIS	A	16	41.388	10.216	16.469	1.00	38.72	A	N

FIGURE 9 - 2

ATOM	130	C	HIS	A	16	43.916	8.854	20.115	1.00	30.78	A	C
ATOM	131	O	HIS	A	16	43.917	10.087	20.052	1.00	29.88	A	O
ATOM	132	N	SER	A	17	43.537	8.199	21.205	1.00	30.04	A	N
ATOM	133	CA	SER	A	17	43.054	8.912	22.381	1.00	30.19	A	C
ATOM	134	CB	SER	A	17	42.272	7.962	23.281	1.00	31.56	A	C
ATOM	135	OG	SER	A	17	43.099	6.890	23.712	1.00	37.12	A	O
ATOM	136	C	SER	A	17	44.155	9.591	23.196	1.00	28.02	A	C
ATOM	137	O	SER	A	17	43.920	10.650	23.785	1.00	28.65	A	O
ATOM	138	N	SER	A	18	45.343	8.995	23.263	1.00	24.87	A	N
ATOM	139	CA	SER	A	18	46.412	9.638	24.022	1.00	24.92	A	C
ATOM	140	CB	SER	A	18	47.568	8.667	24.325	1.00	24.04	A	C
ATOM	141	OG	SER	A	18	48.271	8.292	23.160	1.00	26.18	A	O
ATOM	142	C	SER	A	18	46.912	10.853	23.234	1.00	23.58	A	C
ATOM	143	O	SER	A	18	47.250	11.885	23.822	1.00	22.83	A	O
ATOM	144	N	VAL	A	19	46.943	10.734	21.905	1.00	23.22	A	N
ATOM	145	CA	VAL	A	19	47.374	11.848	21.064	1.00	22.16	A	C
ATOM	146	CB	VAL	A	19	47.516	11.444	19.568	1.00	21.80	A	C
ATOM	147	CG1	VAL	A	19	47.721	12.691	18.709	1.00	21.11	A	C
ATOM	148	CG2	VAL	A	19	48.712	10.487	19.388	1.00	20.96	A	C
ATOM	149	C	VAL	A	19	46.336	12.963	21.189	1.00	22.14	A	C
ATOM	150	O	VAL	A	19	46.678	14.109	21.468	1.00	20.27	A	O
ATOM	151	N	ALA	A	20	45.067	12.613	20.996	1.00	24.06	A	N
ATOM	152	CA	ALA	A	20	43.975	13.579	21.098	1.00	24.10	A	C
ATOM	153	CB	ALA	A	20	42.638	12.862	21.036	1.00	23.57	A	C
ATOM	154	C	ALA	A	20	44.101	14.344	22.416	1.00	24.49	A	C
ATOM	155	O	ALA	A	20	43.978	15.570	22.452	1.00	23.70	A	O
ATOM	156	N	GLU	A	21	44.366	13.615	23.494	1.00	25.16	A	N
ATOM	157	CA	GLU	A	21	44.513	14.229	24.806	1.00	26.38	A	C
ATOM	158	CB	GLU	A	21	44.634	13.139	25.882	1.00	29.08	A	C
ATOM	159	CG	GLU	A	21	44.643	13.631	27.332	1.00	33.17	A	C
ATOM	160	CD	GLU	A	21	43.513	14.622	27.654	1.00	37.76	A	C
ATOM	161	OE1	GLU	A	21	42.320	14.335	27.358	1.00	40.49	A	O
ATOM	162	OE2	GLU	A	21	43.823	15.693	28.215	1.00	38.04	A	O
ATOM	163	C	GLU	A	21	45.718	15.176	24.842	1.00	25.82	A	C
ATOM	164	O	GLU	A	21	45.599	16.326	25.273	1.00	24.84	A	O
ATOM	165	N	LEU	A	22	46.872	14.708	24.377	1.00	24.48	A	N
ATOM	166	CA	LEU	A	22	48.068	15.547	24.366	1.00	24.06	A	C
ATOM	167	CB	LEU	A	22	49.233	14.779	23.747	1.00	24.45	A	C
ATOM	168	CG	LEU	A	22	50.577	15.481	23.531	1.00	24.83	A	C
ATOM	169	CD1	LEU	A	22	51.042	16.173	24.809	1.00	23.46	A	C
ATOM	170	CD2	LEU	A	22	51.600	14.429	23.068	1.00	23.04	A	C
ATOM	171	C	LEU	A	22	47.797	16.827	23.572	1.00	24.06	A	C
ATOM	172	O	LEU	A	22	48.239	17.917	23.951	1.00	23.44	A	O
ATOM	173	N	ILE	A	23	47.063	16.692	22.472	1.00	23.41	A	N
ATOM	174	CA	ILE	A	23	46.724	17.848	21.642	1.00	25.38	A	C
ATOM	175	CB	ILE	A	23	45.848	17.462	20.424	1.00	25.03	A	C
ATOM	176	CG2	ILE	A	23	45.422	18.723	19.669	1.00	23.51	A	C
ATOM	177	CG1	ILE	A	23	46.611	16.513	19.503	1.00	23.69	A	C
ATOM	178	CD1	ILE	A	23	45.765	15.973	18.387	1.00	23.55	A	C
ATOM	179	C	ILE	A	23	45.918	18.841	22.464	1.00	26.93	A	C
ATOM	180	O	ILE	A	23	46.182	20.044	22.445	1.00	26.59	A	O
ATOM	181	N	LYS	A	24	44.922	18.324	23.179	1.00	28.05	A	N
ATOM	182	CA	LYS	A	24	44.074	19.173	23.996	1.00	28.73	A	C
ATOM	183	CB	LYS	A	24	42.985	18.356	24.696	1.00	30.66	A	C
ATOM	184	CG	LYS	A	24	41.815	19.229	25.111	1.00	34.94	A	C
ATOM	185	CD	LYS	A	24	40.601	18.433	25.579	1.00	38.91	A	C
ATOM	186	CE	LYS	A	24	39.287	19.094	25.099	1.00	40.17	A	C
ATOM	187	NZ	LYS	A	24	39.076	20.525	25.510	1.00	39.57	A	N
ATOM	188	C	LYS	A	24	44.887	19.936	25.023	1.00	27.19	A	C
ATOM	189	O	LYS	A	24	44.660	21.129	25.236	1.00	27.16	A	O
ATOM	190	N	GLY	A	25	45.837	19.253	25.654	1.00	26.00	A	N
ATOM	191	CA	GLY	A	25	46.670	19.902	26.645	1.00	24.59	A	C
ATOM	192	C	GLY	A	25	47.560	20.974	26.038	1.00	25.36	A	C
ATOM	193	O	GLY	A	25	47.803	22.003	26.665	1.00	26.41	A	O
ATOM	194	N	LEU	A	26	48.050	20.738	24.820	1.00	24.53	A	N
ATOM	195	CA	LEU	A	26	48.915	21.703	24.142	1.00	24.27	A	C

FIGURE 9 - 3

ATOM	196	CB	LEU	A	26	49.518	21.086	22.870	1.00	23.24	A	C
ATOM	197	CG	LEU	A	26	50.587	19.999	23.059	1.00	23.26	A	C
ATOM	198	CD1	LEU	A	26	50.912	19.349	21.714	1.00	21.18	A	C
ATOM	199	CD2	LEU	A	26	51.840	20.602	23.689	1.00	22.07	A	C
ATOM	200	C	LEU	A	26	48.169	22.998	23.793	1.00	23.31	A	C
ATOM	201	O	LEU	A	26	48.696	24.087	23.979	1.00	22.24	A	O
ATOM	202	N	ARG	A	27	46.945	22.873	23.290	1.00	23.81	A	N
ATOM	203	CA	ARG	A	27	46.140	24.037	22.932	1.00	23.88	A	C
ATOM	204	CB	ARG	A	27	44.762	23.611	22.427	1.00	23.32	A	C
ATOM	205	CG	ARG	A	27	44.741	22.851	21.128	1.00	26.57	A	C
ATOM	206	CD	ARG	A	27	43.313	22.489	20.770	1.00	27.06	A	C
ATOM	207	NE	ARG	A	27	42.504	23.674	20.505	1.00	30.39	A	N
ATOM	208	CZ	ARG	A	27	42.544	24.374	19.375	1.00	32.04	A	C
ATOM	209	NH1	ARG	A	27	43.356	24.017	18.387	1.00	30.90	A	N
ATOM	210	NH2	ARG	A	27	41.752	25.426	19.224	1.00	31.37	A	N
ATOM	211	C	ARG	A	27	45.930	24.922	24.155	1.00	24.82	A	C
ATOM	212	O	ARG	A	27	45.895	26.145	24.052	1.00	24.98	A	O
ATOM	213	N	GLN	A	28	45.782	24.286	25.311	1.00	26.47	A	N
ATOM	214	CA	GLN	A	28	45.542	24.994	26.566	1.00	28.33	A	C
ATOM	215	CB	GLN	A	28	45.071	24.008	27.637	1.00	30.08	A	C
ATOM	216	CG	GLN	A	28	43.809	23.238	27.299	1.00	33.15	A	C
ATOM	217	CD	GLN	A	28	42.562	24.099	27.344	1.00	34.27	A	C
ATOM	218	OE1	GLN	A	28	42.286	24.754	28.355	1.00	34.67	A	O
ATOM	219	NE2	GLN	A	28	41.797	24.100	26.250	1.00	32.10	A	N
ATOM	220	C	GLN	A	28	46.759	25.740	27.109	1.00	28.85	A	C
ATOM	221	O	GLN	A	28	46.622	26.636	27.944	1.00	29.20	A	O
ATOM	222	N	LEU	A	29	47.942	25.369	26.637	1.00	28.41	A	N
ATOM	223	CA	LEU	A	29	49.173	25.975	27.116	1.00	27.29	A	C
ATOM	224	CB	LEU	A	29	50.389	25.267	26.503	1.00	27.49	A	C
ATOM	225	CG	LEU	A	29	50.579	23.795	26.863	1.00	29.30	A	C
ATOM	226	CD1	LEU	A	29	51.881	23.297	26.249	1.00	28.82	A	C
ATOM	227	CD2	LEU	A	29	50.608	23.627	28.389	1.00	29.57	A	C
ATOM	228	C	LEU	A	29	49.322	27.464	26.891	1.00	26.33	A	C
ATOM	229	O	LEU	A	29	48.897	28.006	25.874	1.00	25.97	A	O
ATOM	230	N	ALA	A	30	49.945	28.114	27.864	1.00	26.07	A	N
ATOM	231	CA	ALA	A	30	50.219	29.535	27.791	1.00	26.78	A	C
ATOM	232	CB	ALA	A	30	50.103	30.168	29.173	1.00	27.51	A	C
ATOM	233	C	ALA	A	30	51.651	29.631	27.284	1.00	26.63	A	C
ATOM	234	O	ALA	A	30	52.591	29.758	28.067	1.00	28.51	A	O
ATOM	235	N	LEU	A	31	51.816	29.550	25.970	1.00	26.79	A	N
ATOM	236	CA	LEU	A	31	53.145	29.618	25.368	1.00	27.63	A	C
ATOM	237	CB	LEU	A	31	53.076	29.304	23.869	1.00	25.11	A	C
ATOM	238	CG	LEU	A	31	52.600	27.885	23.563	1.00	26.13	A	C
ATOM	239	CD1	LEU	A	31	52.642	27.646	22.067	1.00	22.59	A	C
ATOM	240	CD2	LEU	A	31	53.486	26.877	24.324	1.00	24.79	A	C
ATOM	241	C	LEU	A	31	53.792	30.978	25.573	1.00	26.83	A	C
ATOM	242	O	LEU	A	31	53.115	31.999	25.611	1.00	27.18	A	O
ATOM	243	N	PRO	A	32	55.121	31.002	25.702	1.00	26.43	A	N
ATOM	244	CD	PRO	A	32	56.043	29.856	25.780	1.00	28.08	A	C
ATOM	245	CA	PRO	A	32	55.840	32.255	25.906	1.00	27.72	A	C
ATOM	246	CB	PRO	A	32	57.129	31.792	26.564	1.00	28.06	A	C
ATOM	247	CG	PRO	A	32	57.414	30.527	25.808	1.00	26.92	A	C
ATOM	248	C	PRO	A	32	56.101	32.940	24.588	1.00	28.93	A	C
ATOM	249	O	PRO	A	32	56.120	32.293	23.540	1.00	29.89	A	O
ATOM	250	N	SER	A	33	56.303	34.250	24.649	1.00	28.33	A	N
ATOM	251	CA	SER	A	33	56.592	35.029	23.463	1.00	30.67	A	C
ATOM	252	CB	SER	A	33	56.178	36.482	23.691	1.00	32.61	A	C
ATOM	253	OG	SER	A	33	56.600	36.904	24.975	1.00	36.43	A	O
ATOM	254	C	SER	A	33	58.089	34.954	23.185	1.00	29.53	A	C
ATOM	255	O	SER	A	33	58.877	34.703	24.089	1.00	31.31	A	O
ATOM	256	N	GLY	A	34	58.476	35.161	21.932	1.00	28.73	A	N
ATOM	257	CA	GLY	A	34	59.884	35.120	21.575	1.00	28.18	A	C
ATOM	258	C	GLY	A	34	60.517	33.740	21.574	1.00	27.91	A	C
ATOM	259	O	GLY	A	34	61.742	33.622	21.595	1.00	28.24	A	O
ATOM	260	N	VAL	A	35	59.693	32.698	21.530	1.00	28.52	A	N
ATOM	261	CA	VAL	A	35	60.192	31.325	21.529	1.00	27.99	A	C

FIGURE 9 - 4

ATOM	262	CB	VAL	A	35	60.046	30.675	22.931	1.00	29.48	A	C
ATOM	263	CG1	VAL	A	35	60.341	29.177	22.853	1.00	28.79	A	C
ATOM	264	CG2	VAL	A	35	60.982	31.349	23.915	1.00	28.47	A	C
ATOM	265	C	VAL	A	35	59.461	30.443	20.523	1.00	27.27	A	C
ATOM	266	O	VAL	A	35	58.245	30.256	20.612	1.00	26.49	A	O
ATOM	267	N	ASP	A	36	60.195	29.899	19.561	1.00	26.91	A	N
ATOM	268	CA	ASP	A	36	59.560	29.021	18.591	1.00	26.67	A	C
ATOM	269	CB	ASP	A	36	60.441	28.819	17.355	1.00	29.43	A	C
ATOM	270	CG	ASP	A	36	60.608	30.093	16.530	1.00	31.48	A	C
ATOM	271	OD1	ASP	A	36	59.601	30.792	16.278	1.00	32.70	A	O
ATOM	272	OD2	ASP	A	36	61.751	30.387	16.117	1.00	32.67	A	O
ATOM	273	C	ASP	A	36	59.308	27.676	19.271	1.00	25.45	A	C
ATOM	274	O	ASP	A	36	60.078	27.243	20.132	1.00	24.80	A	O
ATOM	275	N	VAL	A	37	58.221	27.027	18.889	1.00	22.78	A	N
ATOM	276	CA	VAL	A	37	57.876	25.742	19.462	1.00	23.34	A	C
ATOM	277	CB	VAL	A	37	56.697	25.859	20.450	1.00	22.08	A	C
ATOM	278	CG1	VAL	A	37	56.411	24.495	21.081	1.00	22.51	A	C
ATOM	279	CG2	VAL	A	37	57.009	26.887	21.510	1.00	19.02	A	C
ATOM	280	C	VAL	A	37	57.486	24.782	18.350	1.00	23.64	A	C
ATOM	281	O	VAL	A	37	56.820	25.167	17.386	1.00	22.03	A	O
ATOM	282	N	ALA	A	38	57.910	23.530	18.488	1.00	23.04	A	N
ATOM	283	CA	ALA	A	38	57.593	22.516	17.494	1.00	23.13	A	C
ATOM	284	CB	ALA	A	38	58.691	22.462	16.431	1.00	21.25	A	C
ATOM	285	C	ALA	A	38	57.444	21.158	18.169	1.00	23.01	A	C
ATOM	286	O	ALA	A	38	57.976	20.930	19.255	1.00	21.43	A	O
ATOM	287	N	VAL	A	39	56.685	20.274	17.530	1.00	22.43	A	N
ATOM	288	CA	VAL	A	39	56.481	18.924	18.029	1.00	20.43	A	C
ATOM	289	CB	VAL	A	39	55.090	18.749	18.699	1.00	21.20	A	C
ATOM	290	CG1	VAL	A	39	55.031	19.541	20.008	1.00	19.08	A	C
ATOM	291	CG2	VAL	A	39	53.992	19.190	17.740	1.00	17.28	A	C
ATOM	292	C	VAL	A	39	56.569	17.985	16.835	1.00	21.10	A	C
ATOM	293	O	VAL	A	39	56.112	18.305	15.729	1.00	19.81	A	O
ATOM	294	N	MET	A	40	57.168	16.825	17.055	1.00	21.30	A	N
ATOM	295	CA	MET	A	40	57.305	15.852	15.990	1.00	22.14	A	C
ATOM	296	CB	MET	A	40	58.780	15.576	15.720	1.00	20.47	A	C
ATOM	297	CG	MET	A	40	59.530	16.775	15.163	1.00	22.33	A	C
ATOM	298	SD	MET	A	40	59.869	18.035	16.366	1.00	19.84	A	S
ATOM	299	CE	MET	A	40	60.409	19.333	15.287	1.00	22.36	A	C
ATOM	300	C	MET	A	40	56.564	14.571	16.365	1.00	22.82	A	C
ATOM	301	O	MET	A	40	57.110	13.684	17.028	1.00	20.11	A	O
ATOM	302	N	PRO	A	41	55.293	14.472	15.957	1.00	22.74	A	N
ATOM	303	CD	PRO	A	41	54.431	15.536	15.413	1.00	23.30	A	C
ATOM	304	CA	PRO	A	41	54.508	13.282	16.274	1.00	23.61	A	C
ATOM	305	CB	PRO	A	41	53.075	13.800	16.231	1.00	23.11	A	C
ATOM	306	CG	PRO	A	41	53.128	14.813	15.162	1.00	22.29	A	C
ATOM	307	C	PRO	A	41	54.741	12.133	15.307	1.00	23.69	A	C
ATOM	308	O	PRO	A	41	55.162	12.336	14.169	1.00	22.83	A	O
ATOM	309	N	PRO	A	42	54.489	10.900	15.765	1.00	24.15	A	N
ATOM	310	CD	PRO	A	42	54.112	10.480	17.126	1.00	23.29	A	C
ATOM	311	CA	PRO	A	42	54.677	9.740	14.902	1.00	22.61	A	C
ATOM	312	CB	PRO	A	42	54.095	8.607	15.730	1.00	23.16	A	C
ATOM	313	CG	PRO	A	42	54.458	9.005	17.109	1.00	23.14	A	C
ATOM	314	C	PRO	A	42	53.900	9.990	13.629	1.00	23.47	A	C
ATOM	315	O	PRO	A	42	52.844	10.619	13.640	1.00	23.31	A	O
ATOM	316	N	CYS	A	43	54.433	9.494	12.530	1.00	24.33	A	N
ATOM	317	CA	CYS	A	43	53.820	9.670	11.237	1.00	27.11	A	C
ATOM	318	CB	CYS	A	43	54.557	8.806	10.222	1.00	30.83	A	C
ATOM	319	SG	CYS	A	43	53.822	8.913	8.615	1.00	42.62	A	S
ATOM	320	C	CYS	A	43	52.308	9.430	11.117	1.00	25.98	A	C
ATOM	321	O	CYS	A	43	51.608	10.235	10.508	1.00	25.11	A	O
ATOM	322	N	LEU	A	44	51.777	8.360	11.697	1.00	25.14	A	N
ATOM	323	CA	LEU	A	44	50.346	8.131	11.521	1.00	27.46	A	C
ATOM	324	CB	LEU	A	44	49.986	6.660	11.792	1.00	29.68	A	C
ATOM	325	CG	LEU	A	44	49.818	6.186	13.221	1.00	30.68	A	C
ATOM	326	CD1	LEU	A	44	49.676	4.677	13.244	1.00	31.49	A	C
ATOM	327	CD2	LEU	A	44	51.010	6.622	14.020	1.00	34.87	A	C

FIGURE 9 - 5

ATOM	328	C	LEU	A	44	49.401	9.059	12.287	1.00	24.91	A	C
ATOM	329	O	LEU	A	44	48.199	8.997	12.084	1.00	23.50	A	O
ATOM	330	N	PHE	A	45	49.943	9.924	13.144	1.00	25.04	A	N
ATOM	331	CA	PHE	A	45	49.125	10.880	13.897	1.00	24.67	A	C
ATOM	332	CB	PHE	A	45	49.378	10.756	15.404	1.00	24.26	A	C
ATOM	333	CG	PHE	A	45	49.107	9.390	15.958	1.00	24.13	A	C
ATOM	334	CD1	PHE	A	45	50.132	8.649	16.539	1.00	23.46	A	C
ATOM	335	CD2	PHE	A	45	47.836	8.832	15.878	1.00	23.92	A	C
ATOM	336	CE1	PHE	A	45	49.902	7.372	17.029	1.00	21.97	A	C
ATOM	337	CE2	PHE	A	45	47.591	7.548	16.365	1.00	24.39	A	C
ATOM	338	CZ	PHE	A	45	48.626	6.817	16.940	1.00	26.49	A	C
ATOM	339	C	PHE	A	45	49.429	12.322	13.483	1.00	24.12	A	C
ATOM	340	O	PHE	A	45	48.890	13.263	14.067	1.00	26.74	A	O
ATOM	341	N	ILE	A	46	50.290	12.497	12.485	1.00	23.68	A	N
ATOM	342	CA	ILE	A	46	50.671	13.835	12.038	1.00	24.20	A	C
ATOM	343	CB	ILE	A	46	51.741	13.774	10.913	1.00	23.87	A	C
ATOM	344	CG2	ILE	A	46	51.928	15.154	10.283	1.00	23.95	A	C
ATOM	345	CG1	ILE	A	46	53.077	13.294	11.500	1.00	25.33	A	C
ATOM	346	CD1	ILE	A	46	54.197	13.119	10.493	1.00	24.22	A	C
ATOM	347	C	ILE	A	46	49.487	14.680	11.581	1.00	25.62	A	C
ATOM	348	O	ILE	A	46	49.361	15.838	11.982	1.00	26.17	A	O
ATOM	349	N	SER	A	47	48.619	14.119	10.746	1.00	24.63	A	N
ATOM	350	CA	SER	A	47	47.458	14.875	10.291	1.00	26.08	A	C
ATOM	351	CB	SER	A	47	46.693	14.100	9.219	1.00	27.67	A	C
ATOM	352	OG	SER	A	47	47.343	14.270	7.967	1.00	33.06	A	O
ATOM	353	C	SER	A	47	46.541	15.226	11.454	1.00	25.19	A	C
ATOM	354	O	SER	A	47	46.039	16.343	11.533	1.00	26.32	A	O
ATOM	355	N	GLN	A	48	46.337	14.280	12.364	1.00	25.96	A	N
ATOM	356	CA	GLN	A	48	45.501	14.524	13.539	1.00	26.76	A	C
ATOM	357	CB	GLN	A	48	45.452	13.274	14.425	1.00	27.53	A	C
ATOM	358	CG	GLN	A	48	44.551	13.400	15.659	1.00	28.85	A	C
ATOM	359	CD	GLN	A	48	44.586	12.149	16.517	1.00	29.71	A	C
ATOM	360	OE1	GLN	A	48	45.041	11.097	16.067	1.00	29.57	A	O
ATOM	361	NE2	GLN	A	48	44.100	12.252	17.752	1.00	30.07	A	N
ATOM	362	C	GLN	A	48	46.058	15.700	14.355	1.00	26.95	A	C
ATOM	363	O	GLN	A	48	45.306	16.569	14.816	1.00	26.69	A	O
ATOM	364	N	VAL	A	49	47.379	15.725	14.528	1.00	24.70	A	N
ATOM	365	CA	VAL	A	49	48.024	16.785	15.296	1.00	22.94	A	C
ATOM	366	CB	VAL	A	49	49.497	16.424	15.590	1.00	22.84	A	C
ATOM	367	CG1	VAL	A	49	50.219	17.602	16.219	1.00	21.67	A	C
ATOM	368	CG2	VAL	A	49	49.545	15.229	16.536	1.00	22.25	A	C
ATOM	369	C	VAL	A	49	47.938	18.149	14.611	1.00	22.11	A	C
ATOM	370	O	VAL	A	49	47.638	19.146	15.262	1.00	21.72	A	O
ATOM	371	N	ILE	A	50	48.190	18.191	13.305	1.00	21.90	A	N
ATOM	372	CA	ILE	A	50	48.124	19.446	12.550	1.00	23.35	A	C
ATOM	373	CB	ILE	A	50	48.538	19.242	11.072	1.00	22.17	A	C
ATOM	374	CG2	ILE	A	50	48.172	20.464	10.250	1.00	20.62	A	C
ATOM	375	CG1	ILE	A	50	50.043	18.953	10.990	1.00	23.59	A	C
ATOM	376	CD1	ILE	A	50	50.559	18.699	9.576	1.00	23.85	A	C
ATOM	377	C	ILE	A	50	46.706	20.024	12.593	1.00	25.09	A	C
ATOM	378	O	ILE	A	50	46.517	21.206	12.872	1.00	25.14	A	O
ATOM	379	N	GLN	A	51	45.713	19.187	12.308	1.00	26.88	A	N
ATOM	380	CA	GLN	A	51	44.322	19.630	12.343	1.00	29.22	A	C
ATOM	381	CB	GLN	A	51	43.386	18.488	11.934	1.00	32.23	A	C
ATOM	382	CG	GLN	A	51	43.185	18.336	10.430	1.00	38.55	A	C
ATOM	383	CD	GLN	A	51	42.375	17.089	10.060	1.00	43.90	A	C
ATOM	384	OE1	GLN	A	51	41.489	16.658	10.813	1.00	44.08	A	O
ATOM	385	NE2	GLN	A	51	42.668	16.513	8.884	1.00	45.38	A	N
ATOM	386	C	GLN	A	51	43.965	20.106	13.750	1.00	28.03	A	C
ATOM	387	O	GLN	A	51	43.331	21.142	13.915	1.00	28.31	A	O
ATOM	388	N	GLY	A	52	44.401	19.350	14.755	1.00	27.06	A	N
ATOM	389	CA	GLY	A	52	44.110	19.682	16.141	1.00	24.88	A	C
ATOM	390	C	GLY	A	52	44.729	20.948	16.718	1.00	25.06	A	C
ATOM	391	O	GLY	A	52	44.094	21.625	17.528	1.00	23.33	A	O
ATOM	392	N	LEU	A	53	45.958	21.268	16.317	1.00	24.55	A	N
ATOM	393	CA	LEU	A	53	46.646	22.452	16.826	1.00	25.70	A	C

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ATOM	394	CB	LEU	A	53	48.155	22.210	16.887	1.00	24.94	A	C
ATOM	395	CG	LEU	A	53	48.644	21.086	17.794	1.00	24.27	A	C
ATOM	396	CD1	LEU	A	53	50.142	20.920	17.653	1.00	23.03	A	C
ATOM	397	CD2	LEU	A	53	48.271	21.408	19.226	1.00	25.58	A	C
ATOM	398	C	LEU	A	53	46.380	23.665	15.953	1.00	28.37	A	C
ATOM	399	O	LEU	A	53	47.108	24.659	16.012	1.00	29.40	A	O
ATOM	400	N	ALA	A	54	45.334	23.580	15.138	1.00	30.32	A	N
ATOM	401	CA	ALA	A	54	44.975	24.670	14.237	1.00	31.21	A	C
ATOM	402	CB	ALA	A	54	43.709	24.301	13.449	1.00	31.81	A	C
ATOM	403	C	ALA	A	54	44.757	25.973	15.004	1.00	31.21	A	C
ATOM	404	O	ALA	A	54	43.897	26.047	15.881	1.00	31.23	A	O
ATOM	405	N	GLY	A	55	45.545	26.991	14.671	1.00	30.28	A	N
ATOM	406	CA	GLY	A	55	45.414	28.280	15.324	1.00	30.20	A	C
ATOM	407	C	GLY	A	55	46.478	28.514	16.367	1.00	30.23	A	C
ATOM	408	O	GLY	A	55	46.780	29.661	16.711	1.00	32.26	A	O
ATOM	409	N	LYS	A	56	47.051	27.427	16.873	1.00	29.47	A	N
ATOM	410	CA	LYS	A	56	48.091	27.517	17.896	1.00	27.92	A	C
ATOM	411	CB	LYS	A	56	48.127	26.219	18.705	1.00	27.80	A	C
ATOM	412	CG	LYS	A	56	48.816	26.347	20.042	1.00	28.80	A	C
ATOM	413	CD	LYS	A	56	47.954	27.118	21.021	1.00	26.93	A	C
ATOM	414	CE	LYS	A	56	48.641	27.226	22.373	1.00	28.62	A	C
ATOM	415	NZ	LYS	A	56	47.749	27.826	23.385	1.00	29.53	A	N
ATOM	416	C	LYS	A	56	49.464	27.762	17.258	1.00	27.62	A	C
ATOM	417	O	LYS	A	56	49.773	27.193	16.205	1.00	26.37	A	O
ATOM	418	N	ALA	A	57	50.287	28.592	17.895	1.00	25.66	A	N
ATOM	419	CA	ALA	A	57	51.610	28.898	17.364	1.00	25.87	A	C
ATOM	420	CB	ALA	A	57	52.103	30.254	17.910	1.00	26.25	A	C
ATOM	421	C	ALA	A	57	52.646	27.806	17.650	1.00	25.60	A	C
ATOM	422	O	ALA	A	57	53.644	28.041	18.325	1.00	24.35	A	O
ATOM	423	N	ILE	A	58	52.391	26.611	17.124	1.00	26.25	A	N
ATOM	424	CA	ILE	A	58	53.284	25.460	17.278	1.00	25.96	A	C
ATOM	425	CB	ILE	A	58	52.657	24.376	18.188	1.00	24.80	A	C
ATOM	426	CG2	ILE	A	58	53.594	23.175	18.298	1.00	22.13	A	C
ATOM	427	CG1	ILE	A	58	52.361	24.948	19.573	1.00	24.95	A	C
ATOM	428	CD1	ILE	A	58	51.652	23.959	20.484	1.00	24.00	A	C
ATOM	429	C	ILE	A	58	53.502	24.833	15.893	1.00	26.05	A	C
ATOM	430	O	ILE	A	58	52.539	24.563	15.179	1.00	25.73	A	O
ATOM	431	N	ASP	A	59	54.752	24.614	15.497	1.00	25.98	A	N
ATOM	432	CA	ASP	A	59	55.004	23.990	14.201	1.00	26.89	A	C
ATOM	433	CB	ASP	A	59	56.322	24.465	13.606	1.00	27.67	A	C
ATOM	434	CG	ASP	A	59	56.263	25.893	13.165	1.00	29.93	A	C
ATOM	435	OD1	ASP	A	59	55.302	26.250	12.455	1.00	34.11	A	O
ATOM	436	OD2	ASP	A	59	57.170	26.656	13.521	1.00	33.21	A	O
ATOM	437	C	ASP	A	59	55.033	22.477	14.333	1.00	25.91	A	C
ATOM	438	O	ASP	A	59	55.475	21.940	15.343	1.00	24.36	A	O
ATOM	439	N	VAL	A	60	54.546	21.791	13.311	1.00	25.82	A	N
ATOM	440	CA	VAL	A	60	54.534	20.341	13.334	1.00	25.21	A	C
ATOM	441	CB	VAL	A	60	53.136	19.804	12.998	1.00	25.57	A	C
ATOM	442	CG1	VAL	A	60	53.157	18.280	12.957	1.00	25.92	A	C
ATOM	443	CG2	VAL	A	60	52.130	20.303	14.032	1.00	25.79	A	C
ATOM	444	C	VAL	A	60	55.545	19.804	12.329	1.00	25.49	A	C
ATOM	445	O	VAL	A	60	55.601	20.256	11.183	1.00	23.75	A	O
ATOM	446	N	GLY	A	61	56.355	18.853	12.778	1.00	26.73	A	N
ATOM	447	CA	GLY	A	61	57.353	18.249	11.913	1.00	26.23	A	C
ATOM	448	C	GLY	A	61	57.308	16.738	12.046	1.00	26.06	A	C
ATOM	449	O	GLY	A	61	56.562	16.213	12.866	1.00	26.38	A	O
ATOM	450	N	ALA	A	62	58.098	16.036	11.240	1.00	26.07	A	N
ATOM	451	CA	ALA	A	62	58.135	14.580	11.286	1.00	23.16	A	C
ATOM	452	CB	ALA	A	62	58.059	14.017	9.877	1.00	23.35	A	C
ATOM	453	C	ALA	A	62	59.406	14.093	11.979	1.00	23.28	A	C
ATOM	454	O	ALA	A	62	60.355	14.849	12.168	1.00	22.90	A	O
ATOM	455	N	GLN	A	63	59.413	12.823	12.362	1.00	23.25	A	N
ATOM	456	CA	GLN	A	63	60.554	12.227	13.036	1.00	22.38	A	C
ATOM	457	CB	GLN	A	63	60.067	11.157	14.013	1.00	20.35	A	C
ATOM	458	CG	GLN	A	63	59.297	11.681	15.212	1.00	20.79	A	C
ATOM	459	CD	GLN	A	63	58.715	10.552	16.046	1.00	22.65	A	C

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ATOM	460	OE1	GLN	A	63	59.292	9.466	16.123	1.00	19.63	A	O
ATOM	461	NE2	GLN	A	63	57.571	10.807	16.684	1.00	21.92	A	N
ATOM	462	C	GLN	A	63	61.512	11.599	12.029	1.00	23.34	A	C
ATOM	463	O	GLN	A	63	62.659	11.273	12.359	1.00	23.09	A	O
ATOM	464	N	ASN	A	64	61.026	11.434	10.803	1.00	23.88	A	N
ATOM	465	CA	ASN	A	64	61.801	10.831	9.725	1.00	24.44	A	C
ATOM	466	CB	ASN	A	64	61.890	9.319	9.956	1.00	25.57	A	C
ATOM	467	CG	ASN	A	64	62.719	8.606	8.904	1.00	25.55	A	C
ATOM	468	OD1	ASN	A	64	63.854	8.974	8.630	1.00	23.38	A	O
ATOM	469	ND2	ASN	A	64	62.149	7.567	8.323	1.00	26.00	A	N
ATOM	470	C	ASN	A	64	61.158	11.123	8.368	1.00	24.39	A	C
ATOM	471	O	ASN	A	64	59.980	11.479	8.292	1.00	23.70	A	O
ATOM	472	N	SER	A	65	61.955	11.011	7.308	1.00	24.04	A	N
ATOM	473	CA	SER	A	65	61.486	11.224	5.941	1.00	22.98	A	C
ATOM	474	CB	SER	A	65	61.527	12.716	5.563	1.00	22.99	A	C
ATOM	475	OG	SER	A	65	62.804	13.286	5.775	1.00	25.38	A	O
ATOM	476	C	SER	A	65	62.329	10.383	4.978	1.00	21.52	A	C
ATOM	477	O	SER	A	65	63.399	9.899	5.342	1.00	22.53	A	O
ATOM	478	N	ALA	A	66	61.839	10.195	3.754	1.00	21.07	A	N
ATOM	479	CA	ALA	A	66	62.537	9.367	2.765	1.00	20.52	A	C
ATOM	480	CB	ALA	A	66	61.538	8.902	1.684	1.00	21.86	A	C
ATOM	481	C	ALA	A	66	63.767	9.994	2.100	1.00	20.09	A	C
ATOM	482	O	ALA	A	66	63.964	11.211	2.129	1.00	19.65	A	O
ATOM	483	N	VAL	A	67	64.591	9.140	1.499	1.00	20.22	A	N
ATOM	484	CA	VAL	A	67	65.792	9.581	0.804	1.00	21.42	A	C
ATOM	485	CB	VAL	A	67	66.744	8.396	0.531	1.00	21.63	A	C
ATOM	486	CG1	VAL	A	67	67.335	7.894	1.832	1.00	19.64	A	C
ATOM	487	CG2	VAL	A	67	66.001	7.283	-0.175	1.00	18.78	A	C
ATOM	488	C	VAL	A	67	65.453	10.263	-0.527	1.00	22.32	A	C
ATOM	489	O	VAL	A	67	66.295	10.946	-1.107	1.00	23.21	A	O
ATOM	490	N	GLU	A	68	64.225	10.070	-1.007	1.00	22.38	A	N
ATOM	491	CA	GLU	A	68	63.771	10.681	-2.261	1.00	25.20	A	C
ATOM	492	CB	GLU	A	68	63.180	9.615	-3.203	1.00	26.65	A	C
ATOM	493	CG	GLU	A	68	64.239	8.682	-3.815	1.00	29.97	A	C
ATOM	494	CD	GLU	A	68	63.664	7.402	-4.441	1.00	32.45	A	C
ATOM	495	OE1	GLU	A	68	62.452	7.358	-4.744	1.00	33.80	A	O
ATOM	496	OE2	GLU	A	68	64.438	6.432	-4.652	1.00	33.75	A	O
ATOM	497	C	GLU	A	68	62.734	11.753	-1.932	1.00	24.72	A	C
ATOM	498	O	GLU	A	68	61.895	11.573	-1.056	1.00	25.16	A	O
ATOM	499	N	PRO	A	69	62.786	12.893	-2.627	1.00	24.68	A	N
ATOM	500	CD	PRO	A	69	63.840	13.291	-3.577	1.00	22.08	A	C
ATOM	501	CA	PRO	A	69	61.842	13.994	-2.381	1.00	24.13	A	C
ATOM	502	CB	PRO	A	69	62.509	15.173	-3.081	1.00	24.61	A	C
ATOM	503	CG	PRO	A	69	63.240	14.507	-4.231	1.00	21.89	A	C
ATOM	504	C	PRO	A	69	60.366	13.853	-2.782	1.00	24.01	A	C
ATOM	505	O	PRO	A	69	59.476	14.236	-2.022	1.00	22.76	A	O
ATOM	506	N	MET	A	70	60.104	13.308	-3.964	1.00	24.45	A	N
ATOM	507	CA	MET	A	70	58.734	13.184	-4.454	1.00	24.73	A	C
ATOM	508	CB	MET	A	70	58.705	13.542	-5.942	1.00	25.11	A	C
ATOM	509	CG	MET	A	70	59.382	14.867	-6.266	1.00	25.32	A	C
ATOM	510	SD	MET	A	70	58.694	16.222	-5.341	1.00	22.46	A	S
ATOM	511	CE	MET	A	70	57.273	16.597	-6.327	1.00	24.68	A	C
ATOM	512	C	MET	A	70	58.068	11.824	-4.248	1.00	24.57	A	C
ATOM	513	O	MET	A	70	58.725	10.848	-3.898	1.00	22.32	A	O
ATOM	514	N	GLN	A	71	56.755	11.778	-4.465	1.00	23.73	A	N
ATOM	515	CA	GLN	A	71	55.998	10.537	-4.331	1.00	26.34	A	C
ATOM	516	CB	GLN	A	71	54.521	10.766	-4.672	1.00	26.99	A	C
ATOM	517	CG	GLN	A	71	53.848	11.859	-3.841	1.00	27.16	A	C
ATOM	518	CD	GLN	A	71	52.355	11.970	-4.108	1.00	28.65	A	C
ATOM	519	OE1	GLN	A	71	51.752	13.031	-3.907	1.00	31.52	A	O
ATOM	520	NE2	GLN	A	71	51.744	10.871	-4.546	1.00	27.09	A	N
ATOM	521	C	GLN	A	71	56.605	9.524	-5.297	1.00	26.14	A	C
ATOM	522	O	GLN	A	71	57.031	9.886	-6.390	1.00	25.94	A	O
ATOM	523	N	GLY	A	72	56.659	8.258	-4.899	1.00	27.89	A	N
ATOM	524	CA	GLY	A	72	57.249	7.264	-5.781	1.00	27.30	A	C
ATOM	525	C	GLY	A	72	57.155	5.834	-5.294	1.00	28.77	A	C

FIGURE 9 - 8

ATOM	526	O	GLY	A	72	56.314	5.511	-4.450	1.00	28.92	A	O
ATOM	527	N	ALA	A	73	58.030	4.982	-5.824	1.00	28.75	A	N
ATOM	528	CA	ALA	A	73	58.042	3.566	-5.482	1.00	29.81	A	C
ATOM	529	CB	ALA	A	73	58.324	2.742	-6.736	1.00	29.64	A	C
ATOM	530	C	ALA	A	73	58.980	3.124	-4.359	1.00	30.03	A	C
ATOM	531	O	ALA	A	73	59.935	2.369	-4.589	1.00	30.59	A	O
ATOM	532	N	LEU	A	74	58.715	3.591	-3.143	1.00	29.48	A	N
ATOM	533	CA	LEU	A	74	59.508	3.188	-1.986	1.00	28.80	A	C
ATOM	534	CB	LEU	A	74	60.400	4.334	-1.493	1.00	28.10	A	C
ATOM	535	CG	LEU	A	74	61.759	4.578	-2.174	1.00	29.21	A	C
ATOM	536	CD1	LEU	A	74	62.498	5.675	-1.403	1.00	27.99	A	C
ATOM	537	CD2	LEU	A	74	62.614	3.309	-2.181	1.00	24.16	A	C
ATOM	538	C	LEU	A	74	58.527	2.756	-0.892	1.00	28.20	A	C
ATOM	539	O	LEU	A	74	58.114	3.556	-0.048	1.00	28.41	A	O
ATOM	540	N	THR	A	75	58.143	1.482	-0.934	1.00	27.36	A	N
ATOM	541	CA	THR	A	75	57.196	0.924	0.019	1.00	25.34	A	C
ATOM	542	CB	THR	A	75	57.040	-0.597	-0.158	1.00	25.81	A	C
ATOM	543	OG1	THR	A	75	56.560	-0.884	-1.478	1.00	26.58	A	O
ATOM	544	CG2	THR	A	75	56.050	-1.141	0.853	1.00	25.10	A	C
ATOM	545	C	THR	A	75	57.567	1.192	1.469	1.00	25.01	A	C
ATOM	546	O	THR	A	75	58.694	0.909	1.908	1.00	24.11	A	O
ATOM	547	N	GLY	A	76	56.604	1.742	2.202	1.00	22.60	A	N
ATOM	548	CA	GLY	A	76	56.807	2.034	3.606	1.00	21.52	A	C
ATOM	549	C	GLY	A	76	57.516	3.336	3.931	1.00	21.66	A	C
ATOM	550	O	GLY	A	76	57.773	3.609	5.103	1.00	21.16	A	O
ATOM	551	N	GLU	A	77	57.831	4.141	2.917	1.00	22.09	A	N
ATOM	552	CA	GLU	A	77	58.519	5.411	3.152	1.00	22.69	A	C
ATOM	553	CB	GLU	A	77	59.735	5.524	2.235	1.00	23.74	A	C
ATOM	554	CG	GLU	A	77	60.800	4.484	2.511	1.00	24.62	A	C
ATOM	555	CD	GLU	A	77	61.387	4.615	3.889	1.00	26.31	A	C
ATOM	556	OE1	GLU	A	77	61.324	3.631	4.664	1.00	29.16	A	O
ATOM	557	OE2	GLU	A	77	61.917	5.703	4.199	1.00	26.87	A	O
ATOM	558	C	GLU	A	77	57.622	6.629	2.959	1.00	22.38	A	C
ATOM	559	O	GLU	A	77	56.618	6.559	2.265	1.00	23.60	A	O
ATOM	560	N	THR	A	78	57.993	7.748	3.573	1.00	21.72	A	N
ATOM	561	CA	THR	A	78	57.204	8.964	3.449	1.00	21.90	A	C
ATOM	562	CB	THR	A	78	56.709	9.455	4.820	1.00	23.71	A	C
ATOM	563	OG1	THR	A	78	55.855	8.465	5.406	1.00	26.17	A	O
ATOM	564	CG2	THR	A	78	55.940	10.768	4.666	1.00	24.14	A	C
ATOM	565	C	THR	A	78	57.966	10.107	2.791	1.00	21.67	A	C
ATOM	566	O	THR	A	78	58.921	10.640	3.359	1.00	21.48	A	O
ATOM	567	N	ALA	A	79	57.523	10.503	1.604	1.00	21.05	A	N
ATOM	568	CA	ALA	A	79	58.186	11.581	0.887	1.00	20.84	A	C
ATOM	569	CB	ALA	A	79	57.632	11.692	-0.512	1.00	21.99	A	C
ATOM	570	C	ALA	A	79	58.067	12.926	1.587	1.00	22.10	A	C
ATOM	571	O	ALA	A	79	56.991	13.311	2.046	1.00	20.64	A	O
ATOM	572	N	PRO	A	80	59.181	13.662	1.688	1.00	22.73	A	N
ATOM	573	CD	PRO	A	80	60.585	13.349	1.375	1.00	21.40	A	C
ATOM	574	CA	PRO	A	80	59.066	14.960	2.354	1.00	22.76	A	C
ATOM	575	CB	PRO	A	80	60.509	15.490	2.356	1.00	22.32	A	C
ATOM	576	CG	PRO	A	80	61.179	14.735	1.231	1.00	22.88	A	C
ATOM	577	C	PRO	A	80	58.070	15.881	1.641	1.00	23.10	A	C
ATOM	578	O	PRO	A	80	57.491	16.765	2.263	1.00	23.07	A	O
ATOM	579	N	SER	A	81	57.861	15.677	0.342	1.00	24.29	A	N
ATOM	580	CA	SER	A	81	56.893	16.508	-0.372	1.00	24.61	A	C
ATOM	581	CB	SER	A	81	56.933	16.253	-1.885	1.00	25.30	A	C
ATOM	582	OG	SER	A	81	56.484	14.951	-2.214	1.00	29.68	A	O
ATOM	583	C	SER	A	81	55.489	16.210	0.181	1.00	23.50	A	C
ATOM	584	O	SER	A	81	54.604	17.065	0.150	1.00	23.06	A	O
ATOM	585	N	GLN	A	82	55.285	14.995	0.680	1.00	22.16	A	N
ATOM	586	CA	GLN	A	82	53.994	14.651	1.266	1.00	22.36	A	C
ATOM	587	CB	GLN	A	82	53.846	13.135	1.416	1.00	22.42	A	C
ATOM	588	CG	GLN	A	82	53.635	12.394	0.094	1.00	24.15	A	C
ATOM	589	CD	GLN	A	82	53.498	10.889	0.283	1.00	23.41	A	C
ATOM	590	OE1	GLN	A	82	54.399	10.229	0.807	1.00	24.37	A	O
ATOM	591	NE2	GLN	A	82	52.367	10.340	-0.147	1.00	24.68	A	N

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ATOM	592	C	GLN	A	82	53.866	15.330	2.635	1.00	21.01	A	C
ATOM	593	O	GLN	A	82	52.788	15.772	3.007	1.00	22.59	A	O
ATOM	594	N	LEU	A	83	54.967	15.411	3.382	1.00	20.73	A	N
ATOM	595	CA	LEU	A	83	54.948	16.060	4.696	1.00	22.14	A	C
ATOM	596	CB	LEU	A	83	56.272	15.832	5.428	1.00	21.53	A	C
ATOM	597	CG	LEU	A	83	56.523	14.397	5.923	1.00	20.86	A	C
ATOM	598	CD1	LEU	A	83	57.922	14.286	6.498	1.00	20.79	A	C
ATOM	599	CD2	LEU	A	83	55.489	14.015	6.965	1.00	18.53	A	C
ATOM	600	C	LEU	A	83	54.664	17.563	4.569	1.00	23.42	A	C
ATOM	601	O	LEU	A	83	53.933	18.128	5.383	1.00	24.38	A	O
ATOM	602	N	ALA	A	84	55.240	18.199	3.547	1.00	23.55	A	N
ATOM	603	CA	ALA	A	84	55.022	19.621	3.294	1.00	24.17	A	C
ATOM	604	CB	ALA	A	84	55.908	20.099	2.144	1.00	20.88	A	C
ATOM	605	C	ALA	A	84	53.548	19.823	2.937	1.00	24.79	A	C
ATOM	606	O	ALA	A	84	52.893	20.723	3.458	1.00	23.13	A	O
ATOM	607	N	ASP	A	85	53.038	18.965	2.054	1.00	26.35	A	N
ATOM	608	CA	ASP	A	85	51.644	19.015	1.620	1.00	29.13	A	C
ATOM	609	CB	ASP	A	85	51.335	17.834	0.693	1.00	32.58	A	C
ATOM	610	CG	ASP	A	85	51.834	18.050	-0.727	1.00	38.34	A	C
ATOM	611	OD1	ASP	A	85	51.920	17.050	-1.488	1.00	40.17	A	O
ATOM	612	OD2	ASP	A	85	52.126	19.216	-1.093	1.00	39.51	A	O
ATOM	613	C	ASP	A	85	50.622	19.011	2.762	1.00	28.38	A	C
ATOM	614	O	ASP	A	85	49.621	19.714	2.679	1.00	27.74	A	O
ATOM	615	N	VAL	A	86	50.848	18.209	3.805	1.00	27.03	A	N
ATOM	616	CA	VAL	A	86	49.901	18.151	4.921	1.00	26.68	A	C
ATOM	617	CB	VAL	A	86	49.909	16.781	5.651	1.00	26.23	A	C
ATOM	618	CG1	VAL	A	86	49.401	15.700	4.734	1.00	26.80	A	C
ATOM	619	CG2	VAL	A	86	51.301	16.462	6.159	1.00	23.27	A	C
ATOM	620	C	VAL	A	86	50.107	19.220	5.985	1.00	26.52	A	C
ATOM	621	O	VAL	A	86	49.337	19.293	6.938	1.00	27.66	A	O
ATOM	622	N	GLY	A	87	51.153	20.026	5.845	1.00	26.80	A	N
ATOM	623	CA	GLY	A	87	51.391	21.082	6.812	1.00	27.37	A	C
ATOM	624	C	GLY	A	87	52.650	21.014	7.661	1.00	28.04	A	C
ATOM	625	O	GLY	A	87	52.842	21.867	8.522	1.00	29.78	A	O
ATOM	626	N	CYS	A	88	53.504	20.018	7.453	1.00	27.54	A	N
ATOM	627	CA	CYS	A	88	54.737	19.931	8.232	1.00	27.54	A	C
ATOM	628	CB	CYS	A	88	55.379	18.544	8.097	1.00	25.07	A	C
ATOM	629	SG	CYS	A	88	54.443	17.223	8.908	1.00	29.90	A	S
ATOM	630	C	CYS	A	88	55.712	20.991	7.744	1.00	27.31	A	C
ATOM	631	O	CYS	A	88	55.704	21.347	6.560	1.00	26.27	A	O
ATOM	632	N	SER	A	89	56.550	21.491	8.655	1.00	25.97	A	N
ATOM	633	CA	SER	A	89	57.535	22.507	8.304	1.00	25.57	A	C
ATOM	634	CB	SER	A	89	57.131	23.851	8.918	1.00	27.21	A	C
ATOM	635	OG	SER	A	89	56.992	23.755	10.322	1.00	29.26	A	O
ATOM	636	C	SER	A	89	58.973	22.152	8.711	1.00	24.67	A	C
ATOM	637	O	SER	A	89	59.917	22.824	8.316	1.00	23.77	A	O
ATOM	638	N	MET	A	90	59.125	21.092	9.496	1.00	25.09	A	N
ATOM	639	CA	MET	A	90	60.433	20.624	9.967	1.00	24.93	A	C
ATOM	640	CB	MET	A	90	60.676	21.044	11.424	1.00	23.18	A	C
ATOM	641	CG	MET	A	90	60.780	22.542	11.696	1.00	23.06	A	C
ATOM	642	SD	MET	A	90	60.886	22.917	13.481	1.00	17.60	A	S
ATOM	643	CE	MET	A	90	62.486	22.460	13.830	1.00	17.74	A	C
ATOM	644	C	MET	A	90	60.449	19.090	9.915	1.00	25.98	A	C
ATOM	645	O	MET	A	90	59.412	18.456	9.699	1.00	27.26	A	O
ATOM	646	N	VAL	A	91	61.619	18.495	10.118	1.00	25.13	A	N
ATOM	647	CA	VAL	A	91	61.735	17.041	10.135	1.00	23.49	A	C
ATOM	648	CB	VAL	A	91	61.593	16.421	8.715	1.00	24.95	A	C
ATOM	649	CG1	VAL	A	91	62.724	16.888	7.814	1.00	25.63	A	C
ATOM	650	CG2	VAL	A	91	61.591	14.883	8.813	1.00	27.62	A	C
ATOM	651	C	VAL	A	91	63.073	16.645	10.730	1.00	22.75	A	C
ATOM	652	O	VAL	A	91	64.098	17.256	10.439	1.00	22.25	A	O
ATOM	653	N	LEU	A	92	63.054	15.635	11.588	1.00	20.95	A	N
ATOM	654	CA	LEU	A	92	64.273	15.165	12.222	1.00	22.13	A	C
ATOM	655	CB	LEU	A	92	63.950	14.351	13.479	1.00	19.68	A	C
ATOM	656	CG	LEU	A	92	63.164	15.012	14.606	1.00	21.51	A	C
ATOM	657	CD1	LEU	A	92	63.038	14.009	15.756	1.00	18.37	A	C

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ATOM	658	CD2	LEU	A	92	63.867	16.296	15.068	1.00	21.83	A	C
ATOM	659	C	LEU	A	92	65.063	14.291	11.260	1.00	22.03	A	C
ATOM	660	O	LEU	A	92	64.493	13.583	10.439	1.00	21.86	A	O
ATOM	661	N	VAL	A	93	66.383	14.343	11.372	1.00	22.74	A	N
ATOM	662	CA	VAL	A	93	67.240	13.546	10.517	1.00	22.20	A	C
ATOM	663	CB	VAL	A	93	67.667	14.345	9.273	1.00	24.90	A	C
ATOM	664	CG1	VAL	A	93	68.431	13.449	8.320	1.00	26.72	A	C
ATOM	665	CG2	VAL	A	93	66.448	14.913	8.582	1.00	26.54	A	C
ATOM	666	C	VAL	A	93	68.484	13.082	11.272	1.00	21.59	A	C
ATOM	667	O	VAL	A	93	69.117	13.851	11.990	1.00	19.24	A	O
ATOM	668	N	GLY	A	94	68.820	11.808	11.119	1.00	21.88	A	N
ATOM	669	CA	GLY	A	94	70.000	11.281	11.780	1.00	19.89	A	C
ATOM	670	C	GLY	A	94	69.878	11.154	13.284	1.00	21.59	A	C
ATOM	671	O	GLY	A	94	70.874	11.263	13.993	1.00	20.89	A	O
ATOM	672	N	HIS	A	95	68.665	10.936	13.783	1.00	20.35	A	N
ATOM	673	CA	HIS	A	95	68.492	10.779	15.214	1.00	20.73	A	C
ATOM	674	CB	HIS	A	95	67.023	10.535	15.582	1.00	20.59	A	C
ATOM	675	CG	HIS	A	95	66.781	10.481	17.059	1.00	20.82	A	C
ATOM	676	CD2	HIS	A	95	66.172	11.356	17.897	1.00	19.90	A	C
ATOM	677	ND1	HIS	A	95	67.273	9.469	17.854	1.00	18.89	A	N
ATOM	678	CE1	HIS	A	95	66.983	9.725	19.118	1.00	20.99	A	C
ATOM	679	NE2	HIS	A	95	66.317	10.864	19.173	1.00	19.67	A	N
ATOM	680	C	HIS	A	95	69.336	9.583	15.648	1.00	20.75	A	C
ATOM	681	O	HIS	A	95	69.428	8.582	14.942	1.00	20.56	A	O
ATOM	682	N	SER	A	96	69.951	9.710	16.812	1.00	20.97	A	N
ATOM	683	CA	SER	A	96	70.808	8.674	17.369	1.00	22.86	A	C
ATOM	684	CB	SER	A	96	71.102	9.000	18.824	1.00	22.43	A	C
ATOM	685	OG	SER	A	96	71.866	7.970	19.404	1.00	32.09	A	O
ATOM	686	C	SER	A	96	70.234	7.260	17.283	1.00	23.31	A	C
ATOM	687	O	SER	A	96	70.959	6.310	17.012	1.00	23.47	A	O
ATOM	688	N	GLU	A	97	68.933	7.131	17.526	1.00	23.37	A	N
ATOM	689	CA	GLU	A	97	68.261	5.842	17.480	1.00	24.40	A	C
ATOM	690	CB	GLU	A	97	66.821	5.991	18.008	1.00	24.48	A	C
ATOM	691	CG	GLU	A	97	66.736	6.016	19.544	1.00	25.49	A	C
ATOM	692	CD	GLU	A	97	65.596	6.881	20.109	1.00	27.14	A	C
ATOM	693	OE1	GLU	A	97	64.545	7.030	19.441	1.00	26.09	A	O
ATOM	694	OE2	GLU	A	97	65.755	7.396	21.245	1.00	27.01	A	O
ATOM	695	C	GLU	A	97	68.272	5.237	16.075	1.00	24.38	A	C
ATOM	696	O	GLU	A	97	68.481	4.036	15.913	1.00	25.68	A	O
ATOM	697	N	ARG	A	98	68.066	6.059	15.055	1.00	23.13	A	N
ATOM	698	CA	ARG	A	98	68.078	5.536	13.694	1.00	23.18	A	C
ATOM	699	CB	ARG	A	98	67.498	6.566	12.727	1.00	20.73	A	C
ATOM	700	CG	ARG	A	98	66.060	6.970	13.051	1.00	18.77	A	C
ATOM	701	CD	ARG	A	98	65.394	7.645	11.857	1.00	18.93	A	C
ATOM	702	NE	ARG	A	98	65.158	6.711	10.759	1.00	17.29	A	N
ATOM	703	CZ	ARG	A	98	64.170	5.818	10.725	1.00	18.68	A	C
ATOM	704	NH1	ARG	A	98	63.306	5.727	11.729	1.00	17.80	A	N
ATOM	705	NH2	ARG	A	98	64.048	5.005	9.680	1.00	17.77	A	N
ATOM	706	C	ARG	A	98	69.495	5.128	13.262	1.00	25.05	A	C
ATOM	707	O	ARG	A	98	69.680	4.106	12.585	1.00	25.50	A	O
ATOM	708	N	ARG	A	99	70.491	5.915	13.661	1.00	24.25	A	N
ATOM	709	CA	ARG	A	99	71.885	5.628	13.316	1.00	25.21	A	C
ATOM	710	CB	ARG	A	99	72.797	6.789	13.739	1.00	25.41	A	C
ATOM	711	CG	ARG	A	99	72.724	8.067	12.910	1.00	24.27	A	C
ATOM	712	CD	ARG	A	99	73.656	9.106	13.529	1.00	22.41	A	C
ATOM	713	NE	ARG	A	99	73.516	10.446	12.966	1.00	20.97	A	N
ATOM	714	CZ	ARG	A	99	74.212	10.915	11.935	1.00	21.14	A	C
ATOM	715	NH1	ARG	A	99	75.109	10.154	11.331	1.00	18.62	A	N
ATOM	716	NH2	ARG	A	99	74.021	12.162	11.523	1.00	19.85	A	N
ATOM	717	C	ARG	A	99	72.421	4.357	13.982	1.00	25.58	A	C
ATOM	718	O	ARG	A	99	72.998	3.490	13.327	1.00	26.49	A	O
ATOM	719	N	LEU	A	100	72.232	4.267	15.295	1.00	28.13	A	N
ATOM	720	CA	LEU	A	100	72.730	3.144	16.089	1.00	28.79	A	C
ATOM	721	CB	LEU	A	100	73.030	3.625	17.513	1.00	27.60	A	C
ATOM	722	CG	LEU	A	100	73.894	4.890	17.639	1.00	29.65	A	C
ATOM	723	CD1	LEU	A	100	73.920	5.331	19.086	1.00	31.17	A	C

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ATOM	724	CD2	LEU	A	100	75.313	4.643	17.135	1.00	30.34	A	C
ATOM	725	C	LEU	A	100	71.843	1.896	16.142	1.00	29.05	A	C
ATOM	726	O	LEU	A	100	72.358	0.778	16.183	1.00	29.64	A	O
ATOM	727	N	ILE	A	101	70.523	2.063	16.147	1.00	28.75	A	N
ATOM	728	CA	ILE	A	101	69.640	0.896	16.194	1.00	28.97	A	C
ATOM	729	CB	ILE	A	101	68.361	1.169	17.014	1.00	28.00	A	C
ATOM	730	CG2	ILE	A	101	67.420	-0.018	16.917	1.00	27.29	A	C
ATOM	731	CG1	ILE	A	101	68.718	1.413	18.476	1.00	28.26	A	C
ATOM	732	CD1	ILE	A	101	67.511	1.730	19.350	1.00	29.81	A	C
ATOM	733	C	ILE	A	101	69.215	0.399	14.814	1.00	29.21	A	C
ATOM	734	O	ILE	A	101	69.167	-0.807	14.562	1.00	30.84	A	O
ATOM	735	N	LEU	A	102	68.902	1.324	13.921	1.00	29.04	A	N
ATOM	736	CA	LEU	A	102	68.465	0.947	12.588	1.00	28.21	A	C
ATOM	737	CB	LEU	A	102	67.339	1.882	12.143	1.00	26.84	A	C
ATOM	738	CG	LEU	A	102	66.193	1.902	13.163	1.00	30.37	A	C
ATOM	739	CD1	LEU	A	102	65.140	2.953	12.797	1.00	29.87	A	C
ATOM	740	CD2	LEU	A	102	65.574	0.518	13.230	1.00	29.13	A	C
ATOM	741	C	LEU	A	102	69.613	0.959	11.586	1.00	27.84	A	C
ATOM	742	O	LEU	A	102	69.412	0.697	10.411	1.00	27.76	A	O
ATOM	743	N	GLY	A	103	70.816	1.267	12.062	1.00	29.82	A	N
ATOM	744	CA	GLY	A	103	71.985	1.290	11.194	1.00	30.21	A	C
ATOM	745	C	GLY	A	103	71.931	2.246	10.011	1.00	30.66	A	C
ATOM	746	O	GLY	A	103	72.359	1.911	8.905	1.00	31.98	A	O
ATOM	747	N	GLU	A	104	71.422	3.448	10.243	1.00	30.08	A	N
ATOM	748	CA	GLU	A	104	71.305	4.460	9.199	1.00	28.56	A	C
ATOM	749	CB	GLU	A	104	70.196	5.432	9.600	1.00	31.15	A	C
ATOM	750	CG	GLU	A	104	69.598	6.253	8.488	1.00	32.15	A	C
ATOM	751	CD	GLU	A	104	68.150	6.622	8.785	1.00	31.78	A	C
ATOM	752	OE1	GLU	A	104	67.270	5.741	8.687	1.00	32.80	A	O
ATOM	753	OE2	GLU	A	104	67.894	7.787	9.132	1.00	32.07	A	O
ATOM	754	C	GLU	A	104	72.656	5.164	9.110	1.00	28.08	A	C
ATOM	755	O	GLU	A	104	73.150	5.679	10.106	1.00	26.92	A	O
ATOM	756	N	SER	A	105	73.250	5.192	7.922	1.00	27.99	A	N
ATOM	757	CA	SER	A	105	74.566	5.812	7.748	1.00	29.21	A	C
ATOM	758	CB	SER	A	105	75.332	5.100	6.631	1.00	30.66	A	C
ATOM	759	OG	SER	A	105	74.760	5.398	5.369	1.00	30.12	A	O
ATOM	760	C	SER	A	105	74.549	7.311	7.440	1.00	29.08	A	C
ATOM	761	O	SER	A	105	73.495	7.901	7.214	1.00	28.26	A	O
ATOM	762	N	ASP	A	106	75.740	7.909	7.435	1.00	29.22	A	N
ATOM	763	CA	ASP	A	106	75.913	9.328	7.145	1.00	30.37	A	C
ATOM	764	CB	ASP	A	106	77.400	9.709	7.244	1.00	32.57	A	C
ATOM	765	CG	ASP	A	106	77.952	9.553	8.674	1.00	35.47	A	C
ATOM	766	OD1	ASP	A	106	77.221	9.892	9.636	1.00	35.84	A	O
ATOM	767	OD2	ASP	A	106	79.110	9.105	8.842	1.00	35.34	A	O
ATOM	768	C	ASP	A	106	75.369	9.662	5.755	1.00	30.39	A	C
ATOM	769	O	ASP	A	106	74.758	10.716	5.548	1.00	30.92	A	O
ATOM	770	N	GLU	A	107	75.588	8.752	4.813	1.00	28.97	A	N
ATOM	771	CA	GLU	A	107	75.130	8.905	3.437	1.00	28.92	A	C
ATOM	772	CB	GLU	A	107	75.565	7.679	2.628	1.00	32.22	A	C
ATOM	773	CG	GLU	A	107	74.728	7.390	1.386	1.00	38.12	A	C
ATOM	774	CD	GLU	A	107	75.148	8.192	0.178	1.00	41.71	A	C
ATOM	775	OE1	GLU	A	107	75.342	9.433	0.300	1.00	44.63	A	O
ATOM	776	OE2	GLU	A	107	75.274	7.578	-0.905	1.00	43.28	A	O
ATOM	777	C	GLU	A	107	73.604	9.058	3.402	1.00	26.24	A	C
ATOM	778	O	GLU	A	107	73.084	10.013	2.834	1.00	25.49	A	O
ATOM	779	N	VAL	A	108	72.905	8.105	4.014	1.00	24.90	A	N
ATOM	780	CA	VAL	A	108	71.443	8.103	4.093	1.00	23.42	A	C
ATOM	781	CB	VAL	A	108	70.955	6.902	4.927	1.00	22.92	A	C
ATOM	782	CG1	VAL	A	108	69.437	6.964	5.105	1.00	23.73	A	C
ATOM	783	CG2	VAL	A	108	71.374	5.604	4.250	1.00	25.45	A	C
ATOM	784	C	VAL	A	108	70.926	9.395	4.737	1.00	23.04	A	C
ATOM	785	O	VAL	A	108	70.012	10.039	4.219	1.00	23.34	A	O
ATOM	786	N	VAL	A	109	71.516	9.752	5.878	1.00	22.72	A	N
ATOM	787	CA	VAL	A	109	71.164	10.965	6.613	1.00	21.24	A	C
ATOM	788	CB	VAL	A	109	72.064	11.138	7.855	1.00	20.95	A	C
ATOM	789	CG1	VAL	A	109	71.849	12.503	8.481	1.00	20.30	A	C

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ATOM	790	CG2	VAL	A	109	71.770	10.041	8.859	1.00	19.24	A	C
ATOM	791	C	VAL	A	109	71.354	12.171	5.707	1.00	23.17	A	C
ATOM	792	O	VAL	A	109	70.497	13.058	5.639	1.00	22.43	A	O
ATOM	793	N	SER	A	110	72.490	12.195	5.018	1.00	23.24	A	N
ATOM	794	CA	SER	A	110	72.804	13.276	4.094	1.00	25.90	A	C
ATOM	795	CB	SER	A	110	74.147	13.018	3.422	1.00	27.68	A	C
ATOM	796	OG	SER	A	110	74.096	13.380	2.049	1.00	33.96	A	O
ATOM	797	C	SER	A	110	71.728	13.373	3.024	1.00	25.69	A	C
ATOM	798	O	SER	A	110	71.254	14.455	2.705	1.00	26.99	A	O
ATOM	799	N	ARG	A	111	71.357	12.227	2.466	1.00	26.42	A	N
ATOM	800	CA	ARG	A	111	70.337	12.163	1.427	1.00	27.72	A	C
ATOM	801	CB	ARG	A	111	70.155	10.716	0.961	1.00	31.68	A	C
ATOM	802	CG	ARG	A	111	71.310	10.144	0.151	1.00	35.70	A	C
ATOM	803	CD	ARG	A	111	71.239	10.570	-1.294	1.00	38.26	A	C
ATOM	804	NE	ARG	A	111	70.045	10.049	-1.964	1.00	43.07	A	N
ATOM	805	CZ	ARG	A	111	69.804	8.756	-2.184	1.00	43.65	A	C
ATOM	806	NH1	ARG	A	111	70.680	7.836	-1.786	1.00	43.39	A	N
ATOM	807	NH2	ARG	A	111	68.687	8.385	-2.803	1.00	42.86	A	N
ATOM	808	C	ARG	A	111	68.990	12.699	1.915	1.00	26.74	A	C
ATOM	809	O	ARG	A	111	68.348	13.493	1.232	1.00	26.52	A	O
ATOM	810	N	LYS	A	112	68.565	12.257	3.095	1.00	25.15	A	N
ATOM	811	CA	LYS	A	112	67.285	12.684	3.658	1.00	23.99	A	C
ATOM	812	CB	LYS	A	112	66.985	11.875	4.922	1.00	22.91	A	C
ATOM	813	CG	LYS	A	112	66.614	10.425	4.618	1.00	22.66	A	C
ATOM	814	CD	LYS	A	112	66.452	9.598	5.873	1.00	21.50	A	C
ATOM	815	CE	LYS	A	112	65.834	8.243	5.557	1.00	20.70	A	C
ATOM	816	NZ	LYS	A	112	65.572	7.474	6.798	1.00	22.87	A	N
ATOM	817	C	LYS	A	112	67.273	14.179	3.961	1.00	23.35	A	C
ATOM	818	O	LYS	A	112	66.268	14.864	3.749	1.00	22.46	A	O
ATOM	819	N	PHE	A	113	68.399	14.678	4.452	1.00	22.04	A	N
ATOM	820	CA	PHE	A	113	68.522	16.085	4.764	1.00	20.99	A	C
ATOM	821	CB	PHE	A	113	69.919	16.385	5.303	1.00	20.11	A	C
ATOM	822	CG	PHE	A	113	70.123	17.818	5.699	1.00	20.20	A	C
ATOM	823	CD1	PHE	A	113	70.194	18.819	4.735	1.00	19.53	A	C
ATOM	824	CD2	PHE	A	113	70.253	18.166	7.036	1.00	20.00	A	C
ATOM	825	CE1	PHE	A	113	70.396	20.149	5.097	1.00	21.21	A	C
ATOM	826	CE2	PHE	A	113	70.454	19.495	7.409	1.00	22.80	A	C
ATOM	827	CZ	PHE	A	113	70.527	20.489	6.429	1.00	20.17	A	C
ATOM	828	C	PHE	A	113	68.264	16.899	3.507	1.00	21.21	A	C
ATOM	829	O	PHE	A	113	67.409	17.788	3.500	1.00	20.47	A	O
ATOM	830	N	ALA	A	114	69.005	16.591	2.445	1.00	21.11	A	N
ATOM	831	CA	ALA	A	114	68.863	17.305	1.182	1.00	21.87	A	C
ATOM	832	CB	ALA	A	114	69.920	16.825	0.180	1.00	22.02	A	C
ATOM	833	C	ALA	A	114	67.464	17.142	0.596	1.00	23.19	A	C
ATOM	834	O	ALA	A	114	66.884	18.097	0.085	1.00	23.74	A	O
ATOM	835	N	ALA	A	115	66.916	15.933	0.667	1.00	24.08	A	N
ATOM	836	CA	ALA	A	115	65.568	15.696	0.142	1.00	23.92	A	C
ATOM	837	CB	ALA	A	115	65.182	14.231	0.306	1.00	23.96	A	C
ATOM	838	C	ALA	A	115	64.544	16.579	0.857	1.00	24.23	A	C
ATOM	839	O	ALA	A	115	63.700	17.219	0.219	1.00	24.01	A	O
ATOM	840	N	ALA	A	116	64.623	16.610	2.183	1.00	23.50	A	N
ATOM	841	CA	ALA	A	116	63.694	17.393	2.977	1.00	24.08	A	C
ATOM	842	CB	ALA	A	116	63.941	17.144	4.468	1.00	22.52	A	C
ATOM	843	C	ALA	A	116	63.817	18.883	2.652	1.00	24.86	A	C
ATOM	844	O	ALA	A	116	62.811	19.574	2.524	1.00	23.78	A	O
ATOM	845	N	GLN	A	117	65.047	19.367	2.504	1.00	25.50	A	N
ATOM	846	CA	GLN	A	117	65.271	20.779	2.193	1.00	27.82	A	C
ATOM	847	CB	GLN	A	117	66.765	21.152	2.236	1.00	27.90	A	C
ATOM	848	CG	GLN	A	117	67.350	21.393	3.613	1.00	28.25	A	C
ATOM	849	CD	GLN	A	117	68.505	22.403	3.595	1.00	28.24	A	C
ATOM	850	OE1	GLN	A	117	69.410	22.317	2.769	1.00	26.74	A	O
ATOM	851	NE2	GLN	A	117	68.471	23.357	4.518	1.00	25.64	A	N
ATOM	852	C	GLN	A	117	64.738	21.171	0.830	1.00	28.02	A	C
ATOM	853	O	GLN	A	117	64.297	22.298	0.643	1.00	27.95	A	O
ATOM	854	N	SER	A	118	64.785	20.263	-0.135	1.00	27.71	A	N
ATOM	855	CA	SER	A	118	64.300	20.637	-1.456	1.00	29.67	A	C

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ATOM	856	CB	SER	A	118	64.761	19.633	-2.523	1.00	29.29	A	C
ATOM	857	OG	SER	A	118	64.565	18.302	-2.108	1.00	32.45	A	O
ATOM	858	C	SER	A	118	62.792	20.799	-1.468	1.00	29.56	A	C
ATOM	859	O	SER	A	118	62.241	21.429	-2.370	1.00	31.23	A	O
ATOM	860	N	CYS	A	119	62.122	20.245	-0.462	1.00	28.63	A	N
ATOM	861	CA	CYS	A	119	60.670	20.367	-0.373	1.00	27.50	A	C
ATOM	862	CB	CYS	A	119	60.049	19.044	0.086	1.00	28.03	A	C
ATOM	863	SG	CYS	A	119	60.134	17.706	-1.153	1.00	28.40	A	S
ATOM	864	C	CYS	A	119	60.248	21.508	0.564	1.00	27.34	A	C
ATOM	865	O	CYS	A	119	59.090	21.594	0.972	1.00	27.81	A	O
ATOM	866	N	GLY	A	120	61.192	22.381	0.894	1.00	26.88	A	N
ATOM	867	CA	GLY	A	120	60.890	23.508	1.760	1.00	27.00	A	C
ATOM	868	C	GLY	A	120	60.925	23.237	3.255	1.00	27.79	A	C
ATOM	869	O	GLY	A	120	60.708	24.150	4.051	1.00	28.94	A	O
ATOM	870	N	LEU	A	121	61.204	21.999	3.651	1.00	25.39	A	N
ATOM	871	CA	LEU	A	121	61.246	21.662	5.069	1.00	24.49	A	C
ATOM	872	CB	LEU	A	121	61.019	20.155	5.256	1.00	23.15	A	C
ATOM	873	CG	LEU	A	121	59.704	19.556	4.742	1.00	23.30	A	C
ATOM	874	CD1	LEU	A	121	59.696	18.039	4.954	1.00	20.41	A	C
ATOM	875	CD2	LEU	A	121	58.530	20.209	5.469	1.00	19.42	A	C
ATOM	876	C	LEU	A	121	62.572	22.065	5.726	1.00	24.61	A	C
ATOM	877	O	LEU	A	121	63.622	22.090	5.077	1.00	24.07	A	O
ATOM	878	N	VAL	A	122	62.514	22.390	7.012	1.00	23.19	A	N
ATOM	879	CA	VAL	A	122	63.710	22.766	7.760	1.00	23.80	A	C
ATOM	880	CB	VAL	A	122	63.432	23.914	8.759	1.00	24.98	A	C
ATOM	881	CG1	VAL	A	122	64.705	24.256	9.518	1.00	24.55	A	C
ATOM	882	CG2	VAL	A	122	62.898	25.132	8.025	1.00	22.48	A	C
ATOM	883	C	VAL	A	122	64.147	21.540	8.552	1.00	23.29	A	C
ATOM	884	O	VAL	A	122	63.507	21.166	9.529	1.00	21.70	A	O
ATOM	885	N	PRO	A	123	65.230	20.882	8.123	1.00	21.82	A	N
ATOM	886	CD	PRO	A	123	65.947	21.022	6.845	1.00	21.17	A	C
ATOM	887	CA	PRO	A	123	65.679	19.698	8.857	1.00	20.61	A	C
ATOM	888	CB	PRO	A	123	66.605	18.998	7.862	1.00	21.35	A	C
ATOM	889	CG	PRO	A	123	67.149	20.122	7.049	1.00	23.51	A	C
ATOM	890	C	PRO	A	123	66.376	20.001	10.174	1.00	20.10	A	C
ATOM	891	O	PRO	A	123	66.963	21.064	10.355	1.00	20.10	A	O
ATOM	892	N	VAL	A	124	66.273	19.056	11.098	1.00	20.26	A	N
ATOM	893	CA	VAL	A	124	66.907	19.151	12.406	1.00	20.51	A	C
ATOM	894	CB	VAL	A	124	65.894	18.893	13.565	1.00	19.48	A	C
ATOM	895	CG1	VAL	A	124	66.619	18.883	14.900	1.00	19.14	A	C
ATOM	896	CG2	VAL	A	124	64.805	19.958	13.571	1.00	21.02	A	C
ATOM	897	C	VAL	A	124	67.947	18.026	12.386	1.00	20.14	A	C
ATOM	898	O	VAL	A	124	67.628	16.872	12.650	1.00	20.29	A	O
ATOM	899	N	LEU	A	125	69.179	18.360	12.033	1.00	20.32	A	N
ATOM	900	CA	LEU	A	125	70.239	17.369	11.967	1.00	19.33	A	C
ATOM	901	CB	LEU	A	125	71.393	17.891	11.107	1.00	19.81	A	C
ATOM	902	CG	LEU	A	125	72.699	17.083	11.047	1.00	21.27	A	C
ATOM	903	CD1	LEU	A	125	72.470	15.698	10.444	1.00	22.91	A	C
ATOM	904	CD2	LEU	A	125	73.689	17.841	10.213	1.00	21.28	A	C
ATOM	905	C	LEU	A	125	70.735	17.042	13.365	1.00	19.71	A	C
ATOM	906	O	LEU	A	125	71.271	17.906	14.057	1.00	20.26	A	O
ATOM	907	N	CYS	A	126	70.535	15.798	13.787	1.00	18.36	A	N
ATOM	908	CA	CYS	A	126	70.986	15.359	15.102	1.00	19.87	A	C
ATOM	909	CB	CYS	A	126	70.046	14.292	15.665	1.00	19.95	A	C
ATOM	910	SG	CYS	A	126	68.309	14.799	15.734	1.00	25.01	A	S
ATOM	911	C	CYS	A	126	72.382	14.773	14.951	1.00	20.26	A	C
ATOM	912	O	CYS	A	126	72.636	14.003	14.019	1.00	19.41	A	O
ATOM	913	N	VAL	A	127	73.285	15.145	15.855	1.00	20.68	A	N
ATOM	914	CA	VAL	A	127	74.653	14.642	15.817	1.00	20.01	A	C
ATOM	915	CB	VAL	A	127	75.620	15.681	15.190	1.00	20.75	A	C
ATOM	916	CG1	VAL	A	127	75.139	16.075	13.796	1.00	19.95	A	C
ATOM	917	CG2	VAL	A	127	75.716	16.907	16.069	1.00	20.08	A	C
ATOM	918	C	VAL	A	127	75.087	14.333	17.241	1.00	21.23	A	C
ATOM	919	O	VAL	A	127	74.566	14.922	18.188	1.00	22.46	A	O
ATOM	920	N	GLY	A	128	76.026	13.400	17.397	1.00	19.45	A	N
ATOM	921	CA	GLY	A	128	76.496	13.042	18.726	1.00	20.51	A	C

FIGURE 9 - 14

ATOM	922	C	GLY	A	128	77.455	11.862	18.735	1.00	21.45	A	C
ATOM	923	O	GLY	A	128	77.491	11.093	17.777	1.00	20.63	A	O
ATOM	924	N	GLU	A	129	78.221	11.712	19.815	1.00	21.31	A	N
ATOM	925	CA	GLU	A	129	79.189	10.629	19.925	1.00	22.36	A	C
ATOM	926	CB	GLU	A	129	80.581	11.202	20.226	1.00	22.99	A	C
ATOM	927	CG	GLU	A	129	80.876	11.450	21.713	1.00	22.81	A	C
ATOM	928	CD	GLU	A	129	80.434	12.811	22.212	1.00	24.01	A	C
ATOM	929	OE1	GLU	A	129	79.379	13.304	21.760	1.00	23.48	A	O
ATOM	930	OE2	GLU	A	129	81.136	13.382	23.076	1.00	23.22	A	O
ATOM	931	C	GLU	A	129	78.829	9.594	20.996	1.00	23.83	A	C
ATOM	932	O	GLU	A	129	78.200	9.917	22.003	1.00	24.41	A	O
ATOM	933	N	THR	A	130	79.242	8.350	20.777	1.00	24.74	A	N
ATOM	934	CA	THR	A	130	78.980	7.270	21.726	1.00	26.14	A	C
ATOM	935	CB	THR	A	130	79.121	5.883	21.043	1.00	27.45	A	C
ATOM	936	OG1	THR	A	130	80.456	5.714	20.537	1.00	26.95	A	O
ATOM	937	CG2	THR	A	130	78.129	5.766	19.879	1.00	27.81	A	C
ATOM	938	C	THR	A	130	79.935	7.336	22.919	1.00	27.21	A	C
ATOM	939	O	THR	A	130	80.861	8.144	22.941	1.00	27.76	A	O
ATOM	940	N	ARG	A	131	79.695	6.504	23.922	1.00	28.47	A	N
ATOM	941	CA	ARG	A	131	80.557	6.485	25.085	1.00	30.46	A	C
ATOM	942	CB	ARG	A	131	80.114	5.421	26.079	1.00	32.07	A	C
ATOM	943	CG	ARG	A	131	81.134	5.238	27.175	1.00	36.56	A	C
ATOM	944	CD	ARG	A	131	80.673	4.298	28.256	1.00	40.21	A	C
ATOM	945	NE	ARG	A	131	81.463	4.521	29.466	1.00	43.27	A	N
ATOM	946	CZ	ARG	A	131	81.258	3.899	30.622	1.00	44.93	A	C
ATOM	947	NH1	ARG	A	131	80.281	2.998	30.737	1.00	45.87	A	N
ATOM	948	NH2	ARG	A	131	82.022	4.192	31.667	1.00	46.87	A	N
ATOM	949	C	ARG	A	131	81.995	6.197	24.681	1.00	31.02	A	C
ATOM	950	O	ARG	A	131	82.913	6.922	25.063	1.00	32.25	A	O
ATOM	951	N	ALA	A	132	82.186	5.134	23.907	1.00	29.92	A	N
ATOM	952	CA	ALA	A	132	83.512	4.750	23.461	1.00	29.99	A	C
ATOM	953	CB	ALA	A	132	83.438	3.449	22.661	1.00	31.07	A	C
ATOM	954	C	ALA	A	132	84.193	5.833	22.635	1.00	30.21	A	C
ATOM	955	O	ALA	A	132	85.367	6.121	22.844	1.00	30.04	A	O
ATOM	956	N	GLU	A	133	83.466	6.434	21.693	1.00	30.43	A	N
ATOM	957	CA	GLU	A	133	84.053	7.482	20.857	1.00	29.12	A	C
ATOM	958	CB	GLU	A	133	83.024	7.982	19.834	1.00	30.35	A	C
ATOM	959	CG	GLU	A	133	82.484	6.885	18.911	1.00	29.99	A	C
ATOM	960	CD	GLU	A	133	81.501	7.400	17.866	1.00	30.52	A	C
ATOM	961	OE1	GLU	A	133	80.541	8.112	18.226	1.00	29.51	A	O
ATOM	962	OE2	GLU	A	133	81.682	7.080	16.675	1.00	30.64	A	O
ATOM	963	C	GLU	A	133	84.580	8.641	21.718	1.00	29.17	A	C
ATOM	964	O	GLU	A	133	85.686	9.142	21.496	1.00	26.87	A	O
ATOM	965	N	ARG	A	134	83.797	9.049	22.712	1.00	27.71	A	N
ATOM	966	CA	ARG	A	134	84.202	10.129	23.606	1.00	28.85	A	C
ATOM	967	CB	ARG	A	134	83.059	10.493	24.555	1.00	28.22	A	C
ATOM	968	CG	ARG	A	134	83.249	11.810	25.317	1.00	29.74	A	C
ATOM	969	CD	ARG	A	134	82.127	12.030	26.338	1.00	28.01	A	C
ATOM	970	NE	ARG	A	134	82.295	13.255	27.116	1.00	27.65	A	N
ATOM	971	CZ	ARG	A	134	82.032	14.478	26.667	1.00	25.70	A	C
ATOM	972	NH1	ARG	A	134	81.577	14.657	25.433	1.00	24.77	A	N
ATOM	973	NH2	ARG	A	134	82.235	15.525	27.456	1.00	26.29	A	N
ATOM	974	C	ARG	A	134	85.433	9.713	24.418	1.00	30.81	A	C
ATOM	975	O	ARG	A	134	86.396	10.473	24.529	1.00	30.27	A	O
ATOM	976	N	GLU	A	135	85.399	8.511	24.991	1.00	32.23	A	N
ATOM	977	CA	GLU	A	135	86.530	8.017	25.767	1.00	32.91	A	C
ATOM	978	CB	GLU	A	135	86.220	6.633	26.335	1.00	35.01	A	C
ATOM	979	CG	GLU	A	135	85.423	6.684	27.638	1.00	37.98	A	C
ATOM	980	CD	GLU	A	135	84.703	5.378	27.955	1.00	39.91	A	C
ATOM	981	OE1	GLU	A	135	84.012	5.318	28.997	1.00	41.05	A	O
ATOM	982	OE2	GLU	A	135	84.813	4.418	27.164	1.00	40.24	A	O
ATOM	983	C	GLU	A	135	87.748	7.956	24.862	1.00	32.70	A	C
ATOM	984	O	GLU	A	135	88.859	8.278	25.278	1.00	32.55	A	O
ATOM	985	N	ALA	A	136	87.531	7.544	23.618	1.00	31.91	A	N
ATOM	986	CA	ALA	A	136	88.610	7.465	22.639	1.00	31.75	A	C
ATOM	987	CB	ALA	A	136	88.149	6.681	21.407	1.00	28.55	A	C

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ATOM	988	C	ALA	A	136	89.050	8.881	22.241	1.00	31.53	A	C
ATOM	989	O	ALA	A	136	89.965	9.061	21.442	1.00	32.95	A	O
ATOM	990	N	GLY	A	137	88.387	9.878	22.818	1.00	32.61	A	N
ATOM	991	CA	GLY	A	137	88.704	11.270	22.539	1.00	31.69	A	C
ATOM	992	C	GLY	A	137	88.410	11.728	21.125	1.00	31.34	A	C
ATOM	993	O	GLY	A	137	89.127	12.567	20.586	1.00	31.03	A	O
ATOM	994	N	LYS	A	138	87.340	11.209	20.531	1.00	31.03	A	N
ATOM	995	CA	LYS	A	138	87.001	11.564	19.158	1.00	30.58	A	C
ATOM	996	CB	LYS	A	138	86.906	10.281	18.315	1.00	32.89	A	C
ATOM	997	CG	LYS	A	138	88.175	9.416	18.426	1.00	35.67	A	C
ATOM	998	CD	LYS	A	138	88.354	8.382	17.294	1.00	38.93	A	C
ATOM	999	CE	LYS	A	138	87.308	7.249	17.322	1.00	40.48	A	C
ATOM	1000	NZ	LYS	A	138	86.009	7.617	16.656	1.00	40.96	A	N
ATOM	1001	C	LYS	A	138	85.739	12.403	18.993	1.00	29.05	A	C
ATOM	1002	O	LYS	A	138	85.197	12.507	17.888	1.00	28.84	A	O
ATOM	1003	N	THR	A	139	85.284	13.024	20.080	1.00	28.96	A	N
ATOM	1004	CA	THR	A	139	84.074	13.846	20.038	1.00	26.71	A	C
ATOM	1005	CB	THR	A	139	83.917	14.684	21.314	1.00	26.35	A	C
ATOM	1006	OG1	THR	A	139	83.597	13.821	22.414	1.00	26.63	A	O
ATOM	1007	CG2	THR	A	139	82.802	15.715	21.142	1.00	24.81	A	C
ATOM	1008	C	THR	A	139	84.035	14.790	18.842	1.00	27.01	A	C
ATOM	1009	O	THR	A	139	83.104	14.742	18.029	1.00	27.22	A	O
ATOM	1010	N	LEU	A	140	85.043	15.647	18.738	1.00	25.70	A	N
ATOM	1011	CA	LEU	A	140	85.110	16.598	17.644	1.00	26.48	A	C
ATOM	1012	CB	LEU	A	140	86.309	17.539	17.828	1.00	27.47	A	C
ATOM	1013	CG	LEU	A	140	86.282	18.361	19.125	1.00	29.93	A	C
ATOM	1014	CD1	LEU	A	140	87.355	19.426	19.085	1.00	28.77	A	C
ATOM	1015	CD2	LEU	A	140	84.920	19.012	19.286	1.00	30.12	A	C
ATOM	1016	C	LEU	A	140	85.182	15.909	16.287	1.00	25.39	A	C
ATOM	1017	O	LEU	A	140	84.527	16.339	15.343	1.00	24.49	A	O
ATOM	1018	N	GLU	A	141	85.975	14.845	16.189	1.00	25.50	A	N
ATOM	1019	CA	GLU	A	141	86.109	14.111	14.932	1.00	26.95	A	C
ATOM	1020	CB	GLU	A	141	87.073	12.927	15.071	1.00	27.24	A	C
ATOM	1021	CG	GLU	A	141	87.254	12.166	13.762	1.00	32.14	A	C
ATOM	1022	CD	GLU	A	141	87.917	10.806	13.934	1.00	35.40	A	C
ATOM	1023	OE1	GLU	A	141	89.020	10.747	14.524	1.00	36.45	A	O
ATOM	1024	OE2	GLU	A	141	87.335	9.794	13.471	1.00	36.32	A	O
ATOM	1025	C	GLU	A	141	84.763	13.573	14.479	1.00	26.89	A	C
ATOM	1026	O	GLU	A	141	84.409	13.659	13.304	1.00	27.94	A	O
ATOM	1027	N	VAL	A	142	84.023	13.002	15.419	1.00	27.40	A	N
ATOM	1028	CA	VAL	A	142	82.718	12.439	15.115	1.00	26.75	A	C
ATOM	1029	CB	VAL	A	142	82.143	11.686	16.338	1.00	27.33	A	C
ATOM	1030	CG1	VAL	A	142	80.716	11.236	16.062	1.00	27.37	A	C
ATOM	1031	CG2	VAL	A	142	83.015	10.465	16.651	1.00	27.45	A	C
ATOM	1032	C	VAL	A	142	81.735	13.509	14.653	1.00	26.36	A	C
ATOM	1033	O	VAL	A	142	81.099	13.344	13.620	1.00	25.50	A	O
ATOM	1034	N	VAL	A	143	81.610	14.605	15.398	1.00	25.40	A	N
ATOM	1035	CA	VAL	A	143	80.677	15.657	14.999	1.00	26.36	A	C
ATOM	1036	CB	VAL	A	143	80.532	16.767	16.087	1.00	27.76	A	C
ATOM	1037	CG1	VAL	A	143	79.939	16.173	17.355	1.00	29.26	A	C
ATOM	1038	CG2	VAL	A	143	81.878	17.416	16.372	1.00	28.69	A	C
ATOM	1039	C	VAL	A	143	81.087	16.293	13.667	1.00	26.94	A	C
ATOM	1040	O	VAL	A	143	80.232	16.681	12.874	1.00	27.57	A	O
ATOM	1041	N	ALA	A	144	82.389	16.396	13.418	1.00	25.74	A	N
ATOM	1042	CA	ALA	A	144	82.867	16.953	12.157	1.00	27.44	A	C
ATOM	1043	CB	ALA	A	144	84.388	17.144	12.200	1.00	27.27	A	C
ATOM	1044	C	ALA	A	144	82.490	16.013	11.012	1.00	27.04	A	C
ATOM	1045	O	ALA	A	144	82.268	16.442	9.882	1.00	29.25	A	O
ATOM	1046	N	ARG	A	145	82.426	14.724	11.301	1.00	27.56	A	N
ATOM	1047	CA	ARG	A	145	82.066	13.752	10.279	1.00	27.25	A	C
ATOM	1048	CB	ARG	A	145	82.334	12.330	10.791	1.00	26.96	A	C
ATOM	1049	CG	ARG	A	145	82.170	11.216	9.752	1.00	30.84	A	C
ATOM	1050	CD	ARG	A	145	82.402	9.843	10.383	1.00	30.88	A	C
ATOM	1051	NE	ARG	A	145	81.405	9.547	11.411	1.00	34.11	A	N
ATOM	1052	CZ	ARG	A	145	81.687	9.109	12.637	1.00	36.26	A	C
ATOM	1053	NH1	ARG	A	145	82.945	8.906	13.019	1.00	37.82	A	N

FIGURE 9 - 16

ATOM	1054	NH2	ARG	A	145	80.702	8.870	13.493	1.00	40.90	A	N
ATOM	1055	C	ARG	A	145	80.584	13.918	9.927	1.00	27.29	A	C
ATOM	1056	O	ARG	A	145	80.230	14.138	8.771	1.00	28.69	A	O
ATOM	1057	N	GLN	A	146	79.726	13.845	10.939	1.00	27.04	A	N
ATOM	1058	CA	GLN	A	146	78.281	13.943	10.738	1.00	25.27	A	C
ATOM	1059	CB	GLN	A	146	77.570	13.679	12.068	1.00	24.31	A	C
ATOM	1060	CG	GLN	A	146	77.959	12.334	12.664	1.00	24.79	A	C
ATOM	1061	CD	GLN	A	146	77.352	12.066	14.037	1.00	26.11	A	C
ATOM	1062	OE1	GLN	A	146	77.351	12.935	14.916	1.00	23.99	A	O
ATOM	1063	NE2	GLN	A	146	76.854	10.844	14.232	1.00	23.71	A	N
ATOM	1064	C	GLN	A	146	77.817	15.259	10.118	1.00	25.40	A	C
ATOM	1065	O	GLN	A	146	76.833	15.289	9.378	1.00	25.59	A	O
ATOM	1066	N	LEU	A	147	78.519	16.343	10.422	1.00	24.90	A	N
ATOM	1067	CA	LEU	A	147	78.186	17.650	9.859	1.00	25.07	A	C
ATOM	1068	CB	LEU	A	147	78.852	18.764	10.665	1.00	22.74	A	C
ATOM	1069	CG	LEU	A	147	78.400	18.987	12.104	1.00	21.74	A	C
ATOM	1070	CD1	LEU	A	147	79.322	19.987	12.758	1.00	22.89	A	C
ATOM	1071	CD2	LEU	A	147	76.967	19.487	12.122	1.00	24.07	A	C
ATOM	1072	C	LEU	A	147	78.703	17.707	8.423	1.00	25.67	A	C
ATOM	1073	O	LEU	A	147	78.092	18.321	7.544	1.00	25.46	A	O
ATOM	1074	N	GLY	A	148	79.839	17.051	8.203	1.00	27.56	A	N
ATOM	1075	CA	GLY	A	148	80.459	17.032	6.890	1.00	29.17	A	C
ATOM	1076	C	GLY	A	148	79.660	16.381	5.777	1.00	30.48	A	C
ATOM	1077	O	GLY	A	148	79.768	16.800	4.617	1.00	30.01	A	O
ATOM	1078	N	SER	A	149	78.863	15.365	6.098	1.00	29.94	A	N
ATOM	1079	CA	SER	A	149	78.097	14.714	5.050	1.00	32.34	A	C
ATOM	1080	CB	SER	A	149	77.250	13.555	5.607	1.00	35.10	A	C
ATOM	1081	OG	SER	A	149	76.235	14.006	6.492	1.00	37.50	A	O
ATOM	1082	C	SER	A	149	77.215	15.757	4.392	1.00	31.10	A	C
ATOM	1083	O	SER	A	149	77.166	15.867	3.166	1.00	33.27	A	O
ATOM	1084	N	VAL	A	150	76.532	16.545	5.207	1.00	29.54	A	N
ATOM	1085	CA	VAL	A	150	75.668	17.584	4.673	1.00	28.08	A	C
ATOM	1086	CB	VAL	A	150	74.891	18.259	5.796	1.00	27.41	A	C
ATOM	1087	CG1	VAL	A	150	74.033	19.381	5.242	1.00	28.70	A	C
ATOM	1088	CG2	VAL	A	150	74.031	17.226	6.494	1.00	30.30	A	C
ATOM	1089	C	VAL	A	150	76.477	18.633	3.908	1.00	27.76	A	C
ATOM	1090	O	VAL	A	150	76.092	19.049	2.817	1.00	26.92	A	O
ATOM	1091	N	ILE	A	151	77.598	19.058	4.477	1.00	27.72	A	N
ATOM	1092	CA	ILE	A	151	78.435	20.065	3.824	1.00	28.74	A	C
ATOM	1093	CB	ILE	A	151	79.674	20.414	4.699	1.00	28.30	A	C
ATOM	1094	CG2	ILE	A	151	80.762	21.059	3.842	1.00	27.06	A	C
ATOM	1095	CG1	ILE	A	151	79.243	21.321	5.859	1.00	29.37	A	C
ATOM	1096	CD1	ILE	A	151	80.353	21.619	6.879	1.00	29.91	A	C
ATOM	1097	C	ILE	A	151	78.913	19.628	2.440	1.00	29.17	A	C
ATOM	1098	O	ILE	A	151	78.874	20.410	1.486	1.00	28.72	A	O
ATOM	1099	N	ASP	A	152	79.370	18.382	2.332	1.00	29.50	A	N
ATOM	1100	CA	ASP	A	152	79.856	17.863	1.058	1.00	30.02	A	C
ATOM	1101	CB	ASP	A	152	80.384	16.432	1.231	1.00	32.67	A	C
ATOM	1102	CG	ASP	A	152	81.705	16.381	1.981	1.00	36.20	A	C
ATOM	1103	OD1	ASP	A	152	82.707	16.903	1.442	1.00	39.62	A	O
ATOM	1104	OD2	ASP	A	152	81.747	15.823	3.102	1.00	38.19	A	O
ATOM	1105	C	ASP	A	152	78.783	17.878	-0.025	1.00	28.90	A	C
ATOM	1106	O	ASP	A	152	79.093	18.007	-1.207	1.00	28.85	A	O
ATOM	1107	N	GLU	A	153	77.523	17.756	0.373	1.00	28.78	A	N
ATOM	1108	CA	GLU	A	153	76.423	17.737	-0.596	1.00	29.97	A	C
ATOM	1109	CB	GLU	A	153	75.273	16.853	-0.094	1.00	32.44	A	C
ATOM	1110	CG	GLU	A	153	75.682	15.427	0.210	1.00	38.67	A	C
ATOM	1111	CD	GLU	A	153	76.345	14.757	-0.977	1.00	40.99	A	C
ATOM	1112	OE1	GLU	A	153	77.273	13.949	-0.728	1.00	43.21	A	O
ATOM	1113	OE2	GLU	A	153	75.940	15.034	-2.141	1.00	39.50	A	O
ATOM	1114	C	GLU	A	153	75.830	19.088	-0.960	1.00	28.33	A	C
ATOM	1115	O	GLU	A	153	75.524	19.334	-2.125	1.00	27.07	A	O
ATOM	1116	N	LEU	A	154	75.654	19.950	0.035	1.00	25.22	A	N
ATOM	1117	CA	LEU	A	154	75.028	21.248	-0.189	1.00	25.00	A	C
ATOM	1118	CB	LEU	A	154	73.701	21.311	0.569	1.00	24.29	A	C
ATOM	1119	CG	LEU	A	154	72.739	20.121	0.496	1.00	25.26	A	C

FIGURE 9 - 17

ATOM	1120	CD1	LEU	A	154	71.677	20.301	1.579	1.00	25.02	A	C
ATOM	1121	CD2	LEU	A	154	72.103	20.020	-0.880	1.00	25.41	A	C
ATOM	1122	C	LEU	A	154	75.857	22.456	0.220	1.00	24.07	A	C
ATOM	1123	O	LEU	A	154	75.454	23.588	-0.032	1.00	26.23	A	O
ATOM	1124	N	GLY	A	155	76.998	22.225	0.854	1.00	23.88	A	N
ATOM	1125	CA	GLY	A	155	77.829	23.333	1.301	1.00	24.05	A	C
ATOM	1126	C	GLY	A	155	77.322	23.827	2.645	1.00	23.55	A	C
ATOM	1127	O	GLY	A	155	76.157	23.630	2.983	1.00	23.96	A	O
ATOM	1128	N	VAL	A	156	78.178	24.486	3.410	1.00	22.67	A	N
ATOM	1129	CA	VAL	A	156	77.788	24.962	4.727	1.00	23.92	A	C
ATOM	1130	CB	VAL	A	156	78.981	25.628	5.447	1.00	22.95	A	C
ATOM	1131	CG1	VAL	A	156	79.373	26.902	4.725	1.00	23.73	A	C
ATOM	1132	CG2	VAL	A	156	78.623	25.902	6.901	1.00	21.73	A	C
ATOM	1133	C	VAL	A	156	76.606	25.929	4.701	1.00	23.73	A	C
ATOM	1134	O	VAL	A	156	75.936	26.116	5.709	1.00	24.38	A	O
ATOM	1135	N	GLY	A	157	76.347	26.531	3.547	1.00	25.39	A	N
ATOM	1136	CA	GLY	A	157	75.239	27.463	3.431	1.00	26.59	A	C
ATOM	1137	C	GLY	A	157	73.891	26.822	3.717	1.00	28.69	A	C
ATOM	1138	O	GLY	A	157	72.940	27.505	4.107	1.00	29.93	A	O
ATOM	1139	N	ALA	A	158	73.805	25.508	3.537	1.00	27.95	A	N
ATOM	1140	CA	ALA	A	158	72.561	24.781	3.782	1.00	27.95	A	C
ATOM	1141	CB	ALA	A	158	72.738	23.297	3.423	1.00	26.06	A	C
ATOM	1142	C	ALA	A	158	72.100	24.918	5.237	1.00	26.98	A	C
ATOM	1143	O	ALA	A	158	70.908	24.839	5.528	1.00	25.53	A	O
ATOM	1144	N	PHE	A	159	73.049	25.128	6.142	1.00	25.75	A	N
ATOM	1145	CA	PHE	A	159	72.738	25.270	7.563	1.00	25.59	A	C
ATOM	1146	CB	PHE	A	159	74.019	25.157	8.387	1.00	24.12	A	C
ATOM	1147	CG	PHE	A	159	74.489	23.748	8.559	1.00	25.38	A	C
ATOM	1148	CD1	PHE	A	159	73.818	22.882	9.415	1.00	26.14	A	C
ATOM	1149	CD2	PHE	A	159	75.577	23.267	7.844	1.00	26.43	A	C
ATOM	1150	CE1	PHE	A	159	74.221	21.560	9.552	1.00	25.07	A	C
ATOM	1151	CE2	PHE	A	159	75.987	21.939	7.977	1.00	26.60	A	C
ATOM	1152	CZ	PHE	A	159	75.306	21.089	8.831	1.00	25.41	A	C
ATOM	1153	C	PHE	A	159	72.001	26.562	7.905	1.00	25.78	A	C
ATOM	1154	O	PHE	A	159	71.526	26.735	9.023	1.00	26.86	A	O
ATOM	1155	N	ALA	A	160	71.905	27.467	6.941	1.00	25.69	A	N
ATOM	1156	CA	ALA	A	160	71.199	28.717	7.160	1.00	26.51	A	C
ATOM	1157	CB	ALA	A	160	71.514	29.697	6.041	1.00	26.86	A	C
ATOM	1158	C	ALA	A	160	69.696	28.408	7.198	1.00	27.37	A	C
ATOM	1159	O	ALA	A	160	68.897	29.185	7.716	1.00	26.15	A	O
ATOM	1160	N	ARG	A	161	69.317	27.260	6.652	1.00	27.52	A	N
ATOM	1161	CA	ARG	A	161	67.916	26.863	6.655	1.00	28.68	A	C
ATOM	1162	CB	ARG	A	161	67.355	26.927	5.233	1.00	31.19	A	C
ATOM	1163	CG	ARG	A	161	66.920	28.343	4.845	1.00	34.54	A	C
ATOM	1164	CD	ARG	A	161	66.725	28.495	3.354	1.00	38.15	A	C
ATOM	1165	NE	ARG	A	161	67.992	28.735	2.662	1.00	44.59	A	N
ATOM	1166	CZ	ARG	A	161	68.532	29.941	2.465	1.00	46.31	A	C
ATOM	1167	NH1	ARG	A	161	67.921	31.037	2.907	1.00	47.29	A	N
ATOM	1168	NH2	ARG	A	161	69.681	30.054	1.808	1.00	48.04	A	N
ATOM	1169	C	ARG	A	161	67.740	25.481	7.276	1.00	26.99	A	C
ATOM	1170	O	ARG	A	161	67.032	24.618	6.755	1.00	25.86	A	O
ATOM	1171	N	ALA	A	162	68.387	25.306	8.423	1.00	26.87	A	N
ATOM	1172	CA	ALA	A	162	68.348	24.059	9.164	1.00	25.70	A	C
ATOM	1173	CB	ALA	A	162	69.356	23.092	8.593	1.00	25.54	A	C
ATOM	1174	C	ALA	A	162	68.650	24.309	10.634	1.00	26.90	A	C
ATOM	1175	O	ALA	A	162	68.913	25.443	11.043	1.00	27.80	A	O
ATOM	1176	N	VAL	A	163	68.611	23.237	11.417	1.00	26.24	A	N
ATOM	1177	CA	VAL	A	163	68.874	23.291	12.846	1.00	25.08	A	C
ATOM	1178	CB	VAL	A	163	67.559	23.221	13.666	1.00	25.69	A	C
ATOM	1179	CG1	VAL	A	163	67.871	23.148	15.148	1.00	26.56	A	C
ATOM	1180	CG2	VAL	A	163	66.689	24.438	13.372	1.00	26.92	A	C
ATOM	1181	C	VAL	A	163	69.721	22.080	13.197	1.00	23.50	A	C
ATOM	1182	O	VAL	A	163	69.608	21.043	12.565	1.00	24.62	A	O
ATOM	1183	N	VAL	A	164	70.586	22.211	14.189	1.00	23.33	A	N
ATOM	1184	CA	VAL	A	164	71.399	21.077	14.590	1.00	22.31	A	C
ATOM	1185	CB	VAL	A	164	72.899	21.361	14.469	1.00	20.94	A	C

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ATOM	1186	CG1	VAL	A	164	73.683	20.173	14.987	1.00	20.70	A	C
ATOM	1187	CG2	VAL	A	164	73.258	21.636	13.025	1.00	21.81	A	C
ATOM	1188	C	VAL	A	164	71.088	20.756	16.039	1.00	22.34	A	C
ATOM	1189	O	VAL	A	164	70.936	21.662	16.853	1.00	21.99	A	O
ATOM	1190	N	ALA	A	165	70.985	19.469	16.348	1.00	21.11	A	N
ATOM	1191	CA	ALA	A	165	70.708	19.027	17.712	1.00	20.36	A	C
ATOM	1192	CB	ALA	A	165	69.367	18.326	17.783	1.00	20.04	A	C
ATOM	1193	C	ALA	A	165	71.809	18.081	18.166	1.00	21.99	A	C
ATOM	1194	O	ALA	A	165	72.081	17.071	17.513	1.00	21.33	A	O
ATOM	1195	N	TYR	A	166	72.444	18.415	19.283	1.00	21.18	A	N
ATOM	1196	CA	TYR	A	166	73.506	17.580	19.817	1.00	21.78	A	C
ATOM	1197	CB	TYR	A	166	74.591	18.431	20.476	1.00	18.90	A	C
ATOM	1198	CG	TYR	A	166	75.585	17.595	21.246	1.00	18.81	A	C
ATOM	1199	CD1	TYR	A	166	76.396	16.667	20.590	1.00	18.53	A	C
ATOM	1200	CE1	TYR	A	166	77.288	15.866	21.292	1.00	17.92	A	C
ATOM	1201	CD2	TYR	A	166	75.691	17.703	22.632	1.00	18.54	A	C
ATOM	1202	CE2	TYR	A	166	76.586	16.903	23.351	1.00	19.94	A	C
ATOM	1203	CZ	TYR	A	166	77.381	15.988	22.672	1.00	20.01	A	C
ATOM	1204	OH	TYR	A	166	78.277	15.210	23.363	1.00	21.99	A	O
ATOM	1205	C	TYR	A	166	72.993	16.579	20.844	1.00	22.54	A	C
ATOM	1206	O	TYR	A	166	72.445	16.970	21.884	1.00	22.79	A	O
ATOM	1207	N	GLU	A	167	73.175	15.295	20.554	1.00	22.07	A	N
ATOM	1208	CA	GLU	A	167	72.760	14.245	21.482	1.00	23.13	A	C
ATOM	1209	CB	GLU	A	167	72.065	13.092	20.770	1.00	22.55	A	C
ATOM	1210	CG	GLU	A	167	70.927	13.425	19.866	1.00	25.06	A	C
ATOM	1211	CD	GLU	A	167	70.341	12.156	19.271	1.00	25.54	A	C
ATOM	1212	OE1	GLU	A	167	69.662	11.415	20.012	1.00	26.54	A	O
ATOM	1213	OE2	GLU	A	167	70.575	11.888	18.078	1.00	22.15	A	O
ATOM	1214	C	GLU	A	167	73.993	13.649	22.150	1.00	23.01	A	C
ATOM	1215	O	GLU	A	167	74.864	13.100	21.469	1.00	22.75	A	O
ATOM	1216	N	PRO	A	168	74.084	13.737	23.486	1.00	22.25	A	N
ATOM	1217	CD	PRO	A	168	73.207	14.432	24.446	1.00	22.41	A	C
ATOM	1218	CA	PRO	A	168	75.252	13.160	24.156	1.00	22.23	A	C
ATOM	1219	CB	PRO	A	168	75.286	13.910	25.482	1.00	22.75	A	C
ATOM	1220	CG	PRO	A	168	73.806	14.046	25.803	1.00	22.26	A	C
ATOM	1221	C	PRO	A	168	74.992	11.655	24.331	1.00	23.30	A	C
ATOM	1222	O	PRO	A	168	74.706	11.183	25.436	1.00	22.27	A	O
ATOM	1223	N	VAL	A	169	75.079	10.910	23.229	1.00	24.51	A	N
ATOM	1224	CA	VAL	A	169	74.829	9.469	23.253	1.00	24.97	A	C
ATOM	1225	CB	VAL	A	169	75.091	8.838	21.845	1.00	26.37	A	C
ATOM	1226	CG1	VAL	A	169	74.927	7.311	21.899	1.00	27.34	A	C
ATOM	1227	CG2	VAL	A	169	74.111	9.415	20.829	1.00	23.12	A	C
ATOM	1228	C	VAL	A	169	75.676	8.790	24.336	1.00	25.20	A	C
ATOM	1229	O	VAL	A	169	75.271	7.787	24.922	1.00	23.22	A	O
ATOM	1230	N	TRP	A	170	76.842	9.364	24.610	1.00	25.13	A	N
ATOM	1231	CA	TRP	A	170	77.741	8.850	25.635	1.00	25.43	A	C
ATOM	1232	CB	TRP	A	170	79.026	9.678	25.674	1.00	26.14	A	C
ATOM	1233	CG	TRP	A	170	78.810	11.181	25.802	1.00	25.69	A	C
ATOM	1234	CD2	TRP	A	170	78.905	11.973	27.000	1.00	25.72	A	C
ATOM	1235	CE2	TRP	A	170	78.727	13.327	26.624	1.00	24.81	A	C
ATOM	1236	CE3	TRP	A	170	79.127	11.672	28.349	1.00	25.81	A	C
ATOM	1237	CD1	TRP	A	170	78.571	12.065	24.785	1.00	26.18	A	C
ATOM	1238	NE1	TRP	A	170	78.527	13.355	25.270	1.00	24.94	A	N
ATOM	1239	CZ2	TRP	A	170	78.764	14.374	27.548	1.00	25.18	A	C
ATOM	1240	CZ3	TRP	A	170	79.166	12.716	29.269	1.00	26.12	A	C
ATOM	1241	CH2	TRP	A	170	78.985	14.051	28.862	1.00	25.30	A	C
ATOM	1242	C	TRP	A	170	77.091	8.903	27.015	1.00	26.95	A	C
ATOM	1243	O	TRP	A	170	77.519	8.212	27.937	1.00	26.86	A	O
ATOM	1244	N	ALA	A	171	76.063	9.733	27.155	1.00	28.53	A	N
ATOM	1245	CA	ALA	A	171	75.366	9.888	28.424	1.00	31.53	A	C
ATOM	1246	CB	ALA	A	171	75.455	11.331	28.896	1.00	30.64	A	C
ATOM	1247	C	ALA	A	171	73.911	9.487	28.296	1.00	34.29	A	C
ATOM	1248	O	ALA	A	171	73.084	9.840	29.135	1.00	35.05	A	O
ATOM	1249	N	ILE	A	172	73.584	8.757	27.237	1.00	36.78	A	N
ATOM	1250	CA	ILE	A	172	72.207	8.342	27.054	1.00	38.15	A	C
ATOM	1251	CB	ILE	A	172	71.670	8.772	25.656	1.00	38.81	A	C

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ATOM	1252	CG2	ILE	A	172	70.229	8.294	25.468	1.00	39.21	A	C
ATOM	1253	CG1	ILE	A	172	71.696	10.304	25.542	1.00	38.50	A	C
ATOM	1254	CD1	ILE	A	172	71.036	10.850	24.273	1.00	38.17	A	C
ATOM	1255	C	ILE	A	172	72.082	6.843	27.263	1.00	39.10	A	C
ATOM	1256	O	ILE	A	172	72.300	6.046	26.350	1.00	39.16	A	O
ATOM	1257	N	GLY	A	173	71.756	6.482	28.502	1.00	41.09	A	N
ATOM	1258	CA	GLY	A	173	71.572	5.094	28.882	1.00	42.26	A	C
ATOM	1259	C	GLY	A	173	72.851	4.369	29.228	1.00	42.67	A	C
ATOM	1260	O	GLY	A	173	72.910	3.141	29.147	1.00	44.10	A	O
ATOM	1261	N	THR	A	174	73.867	5.117	29.640	1.00	42.67	A	N
ATOM	1262	CA	THR	A	174	75.164	4.532	29.964	1.00	40.83	A	C
ATOM	1263	CB	THR	A	174	76.263	5.246	29.198	1.00	42.40	A	C
ATOM	1264	OG1	THR	A	174	76.254	6.628	29.587	1.00	41.90	A	O
ATOM	1265	CG2	THR	A	174	76.028	5.146	27.693	1.00	42.07	A	C
ATOM	1266	C	THR	A	174	75.491	4.708	31.432	1.00	40.25	A	C
ATOM	1267	O	THR	A	174	76.461	4.135	31.933	1.00	38.57	A	O
ATOM	1268	N	GLY	A	175	74.690	5.520	32.114	1.00	39.49	A	N
ATOM	1269	CA	GLY	A	175	74.955	5.791	33.512	1.00	40.13	A	C
ATOM	1270	C	GLY	A	175	75.710	7.107	33.660	1.00	39.39	A	C
ATOM	1271	O	GLY	A	175	75.597	7.771	34.683	1.00	39.82	A	O
ATOM	1272	N	LEU	A	176	76.476	7.494	32.641	1.00	38.55	A	N
ATOM	1273	CA	LEU	A	176	77.226	8.752	32.692	1.00	36.30	A	C
ATOM	1274	CB	LEU	A	176	78.254	8.816	31.558	1.00	34.97	A	C
ATOM	1275	CG	LEU	A	176	79.221	7.625	31.496	1.00	34.55	A	C
ATOM	1276	CD1	LEU	A	176	80.107	7.741	30.275	1.00	33.13	A	C
ATOM	1277	CD2	LEU	A	176	80.054	7.565	32.768	1.00	33.82	A	C
ATOM	1278	C	LEU	A	176	76.240	9.901	32.557	1.00	36.22	A	C
ATOM	1279	O	LEU	A	176	75.171	9.739	31.962	1.00	36.88	A	O
ATOM	1280	N	THR	A	177	76.593	11.056	33.112	1.00	34.99	A	N
ATOM	1281	CA	THR	A	177	75.726	12.223	33.049	1.00	34.70	A	C
ATOM	1282	CB	THR	A	177	75.237	12.629	34.450	1.00	36.79	A	C
ATOM	1283	OG1	THR	A	177	76.372	12.921	35.271	1.00	37.89	A	O
ATOM	1284	CG2	THR	A	177	74.429	11.492	35.104	1.00	37.23	A	C
ATOM	1285	C	THR	A	177	76.439	13.427	32.440	1.00	33.78	A	C
ATOM	1286	O	THR	A	177	77.624	13.666	32.696	1.00	33.54	A	O
ATOM	1287	N	ALA	A	178	75.711	14.179	31.624	1.00	30.84	A	N
ATOM	1288	CA	ALA	A	178	76.266	15.365	31.010	1.00	28.77	A	C
ATOM	1289	CB	ALA	A	178	75.806	15.481	29.563	1.00	27.66	A	C
ATOM	1290	C	ALA	A	178	75.780	16.559	31.815	1.00	27.19	A	C
ATOM	1291	O	ALA	A	178	74.593	16.678	32.115	1.00	27.90	A	O
ATOM	1292	N	SER	A	179	76.709	17.430	32.179	1.00	25.65	A	N
ATOM	1293	CA	SER	A	179	76.393	18.629	32.936	1.00	24.89	A	C
ATOM	1294	CB	SER	A	179	77.538	18.958	33.891	1.00	25.65	A	C
ATOM	1295	OG	SER	A	179	78.713	19.255	33.157	1.00	26.02	A	O
ATOM	1296	C	SER	A	179	76.234	19.774	31.941	1.00	25.60	A	C
ATOM	1297	O	SER	A	179	76.673	19.680	30.797	1.00	25.30	A	O
ATOM	1298	N	PRO	A	180	75.586	20.866	32.358	1.00	25.86	A	N
ATOM	1299	CD	PRO	A	180	74.732	21.032	33.549	1.00	26.07	A	C
ATOM	1300	CA	PRO	A	180	75.424	21.988	31.426	1.00	26.24	A	C
ATOM	1301	CB	PRO	A	180	74.742	23.043	32.288	1.00	25.91	A	C
ATOM	1302	CG	PRO	A	180	73.829	22.189	33.141	1.00	27.50	A	C
ATOM	1303	C	PRO	A	180	76.762	22.460	30.843	1.00	26.29	A	C
ATOM	1304	O	PRO	A	180	76.845	22.823	29.668	1.00	26.65	A	O
ATOM	1305	N	ALA	A	181	77.808	22.447	31.661	1.00	26.19	A	N
ATOM	1306	CA	ALA	A	181	79.123	22.869	31.197	1.00	26.48	A	C
ATOM	1307	CB	ALA	A	181	80.139	22.743	32.307	1.00	26.08	A	C
ATOM	1308	C	ALA	A	181	79.549	22.024	30.004	1.00	26.39	A	C
ATOM	1309	O	ALA	A	181	79.820	22.553	28.925	1.00	27.82	A	O
ATOM	1310	N	GLN	A	182	79.602	20.712	30.199	1.00	25.31	A	N
ATOM	1311	CA	GLN	A	182	79.996	19.801	29.126	1.00	26.01	A	C
ATOM	1312	CB	GLN	A	182	79.845	18.353	29.595	1.00	26.47	A	C
ATOM	1313	CG	GLN	A	182	80.671	18.017	30.836	1.00	27.70	A	C
ATOM	1314	CD	GLN	A	182	80.371	16.624	31.355	1.00	29.50	A	C
ATOM	1315	OE1	GLN	A	182	79.218	16.303	31.654	1.00	28.37	A	O
ATOM	1316	NE2	GLN	A	182	81.408	15.783	31.461	1.00	28.58	A	N
ATOM	1317	C	GLN	A	182	79.180	20.021	27.845	1.00	25.57	A	C

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ATOM	1318	O	GLN	A	182	79.738	20.034	26.749	1.00	26.05	A	O
ATOM	1319	N	ALA	A	183	77.866	20.189	27.983	1.00	24.98	A	N
ATOM	1320	CA	ALA	A	183	76.999	20.412	26.829	1.00	25.67	A	C
ATOM	1321	CB	ALA	A	183	75.550	20.544	27.269	1.00	25.58	A	C
ATOM	1322	C	ALA	A	183	77.439	21.675	26.110	1.00	26.88	A	C
ATOM	1323	O	ALA	A	183	77.634	21.674	24.889	1.00	28.07	A	O
ATOM	1324	N	GLN	A	184	77.592	22.753	26.871	1.00	27.50	A	N
ATOM	1325	CA	GLN	A	184	78.029	24.032	26.312	1.00	27.76	A	C
ATOM	1326	CB	GLN	A	184	78.218	25.063	27.436	1.00	26.62	A	C
ATOM	1327	CG	GLN	A	184	79.011	26.321	27.072	1.00	25.37	A	C
ATOM	1328	CD	GLN	A	184	78.482	27.054	25.845	1.00	26.50	A	C
ATOM	1329	OE1	GLN	A	184	77.271	27.187	25.650	1.00	26.90	A	O
ATOM	1330	NE2	GLN	A	184	79.394	27.548	25.021	1.00	25.19	A	N
ATOM	1331	C	GLN	A	184	79.340	23.821	25.568	1.00	28.54	A	C
ATOM	1332	O	GLN	A	184	79.524	24.327	24.463	1.00	30.57	A	O
ATOM	1333	N	GLU	A	185	80.242	23.054	26.172	1.00	28.37	A	N
ATOM	1334	CA	GLU	A	185	81.531	22.788	25.563	1.00	27.94	A	C
ATOM	1335	CB	GLU	A	185	82.330	21.817	26.435	1.00	29.22	A	C
ATOM	1336	CG	GLU	A	185	83.761	21.608	25.958	1.00	32.97	A	C
ATOM	1337	CD	GLU	A	185	84.552	20.649	26.839	1.00	34.93	A	C
ATOM	1338	OE1	GLU	A	185	85.771	20.497	26.604	1.00	36.75	A	O
ATOM	1339	OE2	GLU	A	185	83.960	20.042	27.759	1.00	37.73	A	O
ATOM	1340	C	GLU	A	185	81.407	22.234	24.141	1.00	26.91	A	C
ATOM	1341	O	GLU	A	185	82.082	22.713	23.235	1.00	27.03	A	O
ATOM	1342	N	VAL	A	186	80.552	21.229	23.941	1.00	26.38	A	N
ATOM	1343	CA	VAL	A	186	80.379	20.644	22.611	1.00	23.65	A	C
ATOM	1344	CB	VAL	A	186	79.619	19.300	22.666	1.00	23.28	A	C
ATOM	1345	CG1	VAL	A	186	79.531	18.707	21.281	1.00	23.35	A	C
ATOM	1346	CG2	VAL	A	186	80.325	18.331	23.588	1.00	22.62	A	C
ATOM	1347	C	VAL	A	186	79.639	21.607	21.677	1.00	23.04	A	C
ATOM	1348	O	VAL	A	186	80.032	21.773	20.524	1.00	22.61	A	O
ATOM	1349	N	HIS	A	187	78.574	22.241	22.166	1.00	22.81	A	N
ATOM	1350	CA	HIS	A	187	77.832	23.192	21.337	1.00	22.39	A	C
ATOM	1351	CB	HIS	A	187	76.692	23.839	22.120	1.00	21.45	A	C
ATOM	1352	CG	HIS	A	187	75.482	22.968	22.260	1.00	22.41	A	C
ATOM	1353	CD2	HIS	A	187	75.327	21.734	22.794	1.00	22.05	A	C
ATOM	1354	ND1	HIS	A	187	74.228	23.367	21.850	1.00	22.74	A	N
ATOM	1355	CE1	HIS	A	187	73.352	22.418	22.127	1.00	21.44	A	C
ATOM	1356	NE2	HIS	A	187	73.993	21.416	22.700	1.00	23.45	A	N
ATOM	1357	C	HIS	A	187	78.772	24.275	20.824	1.00	23.56	A	C
ATOM	1358	O	HIS	A	187	78.729	24.635	19.653	1.00	23.80	A	O
ATOM	1359	N	ALA	A	188	79.635	24.781	21.699	1.00	24.61	A	N
ATOM	1360	CA	ALA	A	188	80.583	25.809	21.296	1.00	26.21	A	C
ATOM	1361	CB	ALA	A	188	81.414	26.264	22.498	1.00	26.29	A	C
ATOM	1362	C	ALA	A	188	81.492	25.248	20.212	1.00	26.14	A	C
ATOM	1363	O	ALA	A	188	81.704	25.871	19.172	1.00	27.35	A	O
ATOM	1364	N	ALA	A	189	82.020	24.056	20.452	1.00	26.39	A	N
ATOM	1365	CA	ALA	A	189	82.911	23.431	19.483	1.00	26.36	A	C
ATOM	1366	CB	ALA	A	189	83.457	22.134	20.040	1.00	27.40	A	C
ATOM	1367	C	ALA	A	189	82.199	23.175	18.161	1.00	26.38	A	C
ATOM	1368	O	ALA	A	189	82.817	23.250	17.094	1.00	27.20	A	O
ATOM	1369	N	ILE	A	190	80.903	22.871	18.220	1.00	25.44	A	N
ATOM	1370	CA	ILE	A	190	80.154	22.619	16.994	1.00	24.43	A	C
ATOM	1371	CB	ILE	A	190	78.735	22.083	17.279	1.00	23.66	A	C
ATOM	1372	CG2	ILE	A	190	77.883	22.149	16.008	1.00	22.09	A	C
ATOM	1373	CG1	ILE	A	190	78.827	20.640	17.771	1.00	21.03	A	C
ATOM	1374	CD1	ILE	A	190	77.512	20.039	18.135	1.00	21.86	A	C
ATOM	1375	C	ILE	A	190	80.040	23.887	16.163	1.00	24.98	A	C
ATOM	1376	O	ILE	A	190	80.234	23.856	14.951	1.00	24.88	A	O
ATOM	1377	N	ARG	A	191	79.736	25.004	16.816	1.00	25.11	A	N
ATOM	1378	CA	ARG	A	191	79.601	26.272	16.108	1.00	25.21	A	C
ATOM	1379	CB	ARG	A	191	79.106	27.365	17.067	1.00	23.65	A	C
ATOM	1380	CG	ARG	A	191	78.394	28.517	16.374	1.00	21.44	A	C
ATOM	1381	CD	ARG	A	191	77.875	29.516	17.386	1.00	21.68	A	C
ATOM	1382	NE	ARG	A	191	76.857	28.947	18.262	1.00	21.18	A	N
ATOM	1383	CZ	ARG	A	191	75.583	28.770	17.916	1.00	22.25	A	C

FIGURE 9 - 21

ATOM	1384	NH1	ARG	A	191	75.157	29.119	16.705	1.00	18.54	A	N
ATOM	1385	NH2	ARG	A	191	74.729	28.251	18.785	1.00	21.06	A	N
ATOM	1386	C	ARG	A	191	80.945	26.670	15.487	1.00	25.48	A	C
ATOM	1387	O	ARG	A	191	80.998	27.181	14.365	1.00	24.40	A	O
ATOM	1388	N	ALA	A	192	82.025	26.415	16.216	1.00	24.91	A	N
ATOM	1389	CA	ALA	A	192	83.360	26.738	15.735	1.00	26.61	A	C
ATOM	1390	CB	ALA	A	192	84.392	26.399	16.797	1.00	27.30	A	C
ATOM	1391	C	ALA	A	192	83.660	25.984	14.446	1.00	26.91	A	C
ATOM	1392	O	ALA	A	192	84.286	26.527	13.538	1.00	27.38	A	O
ATOM	1393	N	GLN	A	193	83.222	24.731	14.370	1.00	27.46	A	N
ATOM	1394	CA	GLN	A	193	83.433	23.933	13.164	1.00	27.39	A	C
ATOM	1395	CB	GLN	A	193	82.951	22.488	13.366	1.00	28.84	A	C
ATOM	1396	CG	GLN	A	193	83.725	21.743	14.451	1.00	32.03	A	C
ATOM	1397	CD	GLN	A	193	83.852	20.257	14.179	1.00	33.39	A	C
ATOM	1398	OE1	GLN	A	193	84.506	19.528	14.927	1.00	34.59	A	O
ATOM	1399	NE2	GLN	A	193	83.228	19.799	13.105	1.00	36.67	A	N
ATOM	1400	C	GLN	A	193	82.649	24.590	12.038	1.00	27.19	A	C
ATOM	1401	O	GLN	A	193	83.190	24.858	10.964	1.00	27.42	A	O
ATOM	1402	N	LEU	A	194	81.373	24.856	12.297	1.00	25.43	A	N
ATOM	1403	CA	LEU	A	194	80.526	25.504	11.313	1.00	24.72	A	C
ATOM	1404	CB	LEU	A	194	79.103	25.696	11.857	1.00	23.95	A	C
ATOM	1405	CG	LEU	A	194	78.202	24.457	12.004	1.00	25.27	A	C
ATOM	1406	CD1	LEU	A	194	76.838	24.888	12.504	1.00	24.52	A	C
ATOM	1407	CD2	LEU	A	194	78.050	23.747	10.660	1.00	25.88	A	C
ATOM	1408	C	LEU	A	194	81.131	26.854	10.951	1.00	23.26	A	C
ATOM	1409	O	LEU	A	194	81.105	27.256	9.794	1.00	24.92	A	O
ATOM	1410	N	ALA	A	195	81.693	27.537	11.943	1.00	24.08	A	N
ATOM	1411	CA	ALA	A	195	82.304	28.854	11.746	1.00	24.66	A	C
ATOM	1412	CB	ALA	A	195	82.653	29.476	13.110	1.00	25.98	A	C
ATOM	1413	C	ALA	A	195	83.537	28.869	10.831	1.00	24.98	A	C
ATOM	1414	O	ALA	A	195	83.760	29.841	10.111	1.00	23.53	A	O
ATOM	1415	N	ALA	A	196	84.336	27.805	10.860	1.00	24.75	A	N
ATOM	1416	CA	ALA	A	196	85.524	27.735	10.002	1.00	26.30	A	C
ATOM	1417	CB	ALA	A	196	86.381	26.518	10.375	1.00	25.46	A	C
ATOM	1418	C	ALA	A	196	85.123	27.658	8.519	1.00	26.39	A	C
ATOM	1419	O	ALA	A	196	85.923	27.966	7.634	1.00	27.18	A	O
ATOM	1420	N	GLU	A	197	83.890	27.242	8.246	1.00	26.05	A	N
ATOM	1421	CA	GLU	A	197	83.431	27.149	6.863	1.00	25.61	A	C
ATOM	1422	CB	GLU	A	197	82.464	25.968	6.701	1.00	24.27	A	C
ATOM	1423	CG	GLU	A	197	83.048	24.616	7.158	1.00	25.07	A	C
ATOM	1424	CD	GLU	A	197	84.274	24.156	6.353	1.00	23.08	A	C
ATOM	1425	OE1	GLU	A	197	85.253	23.697	6.976	1.00	22.55	A	O
ATOM	1426	OE2	GLU	A	197	84.260	24.231	5.107	1.00	24.35	A	O
ATOM	1427	C	GLU	A	197	82.766	28.468	6.447	1.00	26.00	A	C
ATOM	1428	O	GLU	A	197	82.937	28.924	5.320	1.00	27.03	A	O
ATOM	1429	N	ASN	A	198	82.015	29.074	7.362	1.00	25.11	A	N
ATOM	1430	CA	ASN	A	198	81.354	30.358	7.114	1.00	25.09	A	C
ATOM	1431	CB	ASN	A	198	80.123	30.199	6.212	1.00	23.56	A	C
ATOM	1432	CG	ASN	A	198	79.476	31.550	5.849	1.00	25.67	A	C
ATOM	1433	OD1	ASN	A	198	79.012	32.292	6.725	1.00	25.82	A	O
ATOM	1434	ND2	ASN	A	198	79.448	31.865	4.553	1.00	22.03	A	N
ATOM	1435	C	ASN	A	198	80.930	30.925	8.464	1.00	25.86	A	C
ATOM	1436	O	ASN	A	198	79.975	30.448	9.073	1.00	24.71	A	O
ATOM	1437	N	ALA	A	199	81.650	31.942	8.926	1.00	27.00	A	N
ATOM	1438	CA	ALA	A	199	81.354	32.551	10.217	1.00	29.32	A	C
ATOM	1439	CB	ALA	A	199	82.371	33.648	10.518	1.00	29.39	A	C
ATOM	1440	C	ALA	A	199	79.929	33.104	10.346	1.00	29.29	A	C
ATOM	1441	O	ALA	A	199	79.259	32.855	11.348	1.00	30.16	A	O
ATOM	1442	N	GLU	A	200	79.459	33.842	9.346	1.00	29.71	A	N
ATOM	1443	CA	GLU	A	200	78.116	34.406	9.422	1.00	31.28	A	C
ATOM	1444	CB	GLU	A	200	77.771	35.234	8.173	1.00	34.61	A	C
ATOM	1445	CG	GLU	A	200	76.444	35.985	8.341	1.00	39.99	A	C
ATOM	1446	CD	GLU	A	200	76.172	37.031	7.263	1.00	45.82	A	C
ATOM	1447	OE1	GLU	A	200	77.074	37.864	6.983	1.00	46.88	A	O
ATOM	1448	OE2	GLU	A	200	75.041	37.038	6.704	1.00	47.99	A	O
ATOM	1449	C	GLU	A	200	77.059	33.325	9.619	1.00	30.52	A	C

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ATOM	1450	O	GLU	A	200	76.230	33.419	10.523	1.00	31.49	A	O
ATOM	1451	N	VAL	A	201	77.096	32.292	8.786	1.00	28.73	A	N
ATOM	1452	CA	VAL	A	201	76.133	31.206	8.894	1.00	27.29	A	C
ATOM	1453	CB	VAL	A	201	76.413	30.120	7.834	1.00	28.50	A	C
ATOM	1454	CG1	VAL	A	201	75.519	28.896	8.083	1.00	29.52	A	C
ATOM	1455	CG2	VAL	A	201	76.163	30.695	6.435	1.00	25.40	A	C
ATOM	1456	C	VAL	A	201	76.164	30.569	10.281	1.00	26.11	A	C
ATOM	1457	O	VAL	A	201	75.123	30.270	10.862	1.00	26.64	A	O
ATOM	1458	N	ALA	A	202	77.365	30.375	10.808	1.00	25.34	A	N
ATOM	1459	CA	ALA	A	202	77.543	29.763	12.117	1.00	25.05	A	C
ATOM	1460	CB	ALA	A	202	79.033	29.564	12.391	1.00	22.78	A	C
ATOM	1461	C	ALA	A	202	76.897	30.550	13.261	1.00	24.66	A	C
ATOM	1462	O	ALA	A	202	76.404	29.964	14.220	1.00	24.39	A	O
ATOM	1463	N	LYS	A	203	76.901	31.872	13.162	1.00	24.28	A	N
ATOM	1464	CA	LYS	A	203	76.320	32.699	14.210	1.00	25.27	A	C
ATOM	1465	CB	LYS	A	203	76.766	34.152	14.049	1.00	27.11	A	C
ATOM	1466	CG	LYS	A	203	78.258	34.361	14.204	1.00	31.07	A	C
ATOM	1467	CD	LYS	A	203	78.664	35.800	13.848	1.00	35.87	A	C
ATOM	1468	CE	LYS	A	203	80.189	35.972	13.909	1.00	37.34	A	C
ATOM	1469	NZ	LYS	A	203	80.627	37.296	13.360	1.00	40.28	A	N
ATOM	1470	C	LYS	A	203	74.804	32.637	14.205	1.00	24.60	A	C
ATOM	1471	O	LYS	A	203	74.166	32.913	15.220	1.00	23.69	A	O
ATOM	1472	N	GLY	A	204	74.234	32.261	13.065	1.00	24.21	A	N
ATOM	1473	CA	GLY	A	204	72.792	32.189	12.957	1.00	24.41	A	C
ATOM	1474	C	GLY	A	204	72.149	30.832	13.173	1.00	23.93	A	C
ATOM	1475	O	GLY	A	204	70.958	30.758	13.440	1.00	24.78	A	O
ATOM	1476	N	VAL	A	205	72.920	29.758	13.077	1.00	23.36	A	N
ATOM	1477	CA	VAL	A	205	72.355	28.423	13.239	1.00	23.48	A	C
ATOM	1478	CB	VAL	A	205	73.350	27.337	12.752	1.00	24.84	A	C
ATOM	1479	CG1	VAL	A	205	74.635	27.397	13.572	1.00	23.10	A	C
ATOM	1480	CG2	VAL	A	205	72.703	25.958	12.873	1.00	21.54	A	C
ATOM	1481	C	VAL	A	205	71.920	28.050	14.658	1.00	22.77	A	C
ATOM	1482	O	VAL	A	205	72.721	28.082	15.580	1.00	23.72	A	O
ATOM	1483	N	ARG	A	206	70.655	27.682	14.837	1.00	22.07	A	N
ATOM	1484	CA	ARG	A	206	70.206	27.280	16.166	1.00	22.57	A	C
ATOM	1485	CB	ARG	A	206	68.675	27.248	16.255	1.00	23.65	A	C
ATOM	1486	CG	ARG	A	206	68.029	28.621	16.406	1.00	25.28	A	C
ATOM	1487	CD	ARG	A	206	67.329	29.070	15.137	1.00	27.42	A	C
ATOM	1488	NE	ARG	A	206	65.894	28.795	15.178	1.00	30.23	A	N
ATOM	1489	CZ	ARG	A	206	65.183	28.373	14.132	1.00	31.92	A	C
ATOM	1490	NH1	ARG	A	206	65.772	28.172	12.950	1.00	30.96	A	N
ATOM	1491	NH2	ARG	A	206	63.881	28.146	14.268	1.00	31.21	A	N
ATOM	1492	C	ARG	A	206	70.773	25.900	16.499	1.00	21.98	A	C
ATOM	1493	O	ARG	A	206	70.637	24.963	15.715	1.00	20.78	A	O
ATOM	1494	N	LEU	A	207	71.443	25.792	17.644	1.00	21.95	A	N
ATOM	1495	CA	LEU	A	207	72.007	24.514	18.093	1.00	22.08	A	C
ATOM	1496	CB	LEU	A	207	73.489	24.660	18.461	1.00	19.71	A	C
ATOM	1497	CG	LEU	A	207	74.490	25.127	17.394	1.00	20.62	A	C
ATOM	1498	CD1	LEU	A	207	75.895	25.142	18.004	1.00	20.74	A	C
ATOM	1499	CD2	LEU	A	207	74.443	24.201	16.177	1.00	17.86	A	C
ATOM	1500	C	LEU	A	207	71.217	24.080	19.325	1.00	22.22	A	C
ATOM	1501	O	LEU	A	207	71.295	24.725	20.371	1.00	22.75	A	O
ATOM	1502	N	LEU	A	208	70.462	22.990	19.204	1.00	21.40	A	N
ATOM	1503	CA	LEU	A	208	69.643	22.509	20.313	1.00	21.08	A	C
ATOM	1504	CB	LEU	A	208	68.300	21.997	19.792	1.00	21.22	A	C
ATOM	1505	CG	LEU	A	208	67.640	22.665	18.583	1.00	21.15	A	C
ATOM	1506	CD1	LEU	A	208	66.307	21.983	18.353	1.00	20.46	A	C
ATOM	1507	CD2	LEU	A	208	67.438	24.158	18.806	1.00	22.79	A	C
ATOM	1508	C	LEU	A	208	70.300	21.387	21.110	1.00	22.11	A	C
ATOM	1509	O	LEU	A	208	71.001	20.547	20.547	1.00	21.35	A	O
ATOM	1510	N	TYR	A	209	70.065	21.377	22.421	1.00	19.68	A	N
ATOM	1511	CA	TYR	A	209	70.603	20.328	23.270	1.00	19.72	A	C
ATOM	1512	CB	TYR	A	209	70.756	20.810	24.711	1.00	19.55	A	C
ATOM	1513	CG	TYR	A	209	71.267	19.728	25.628	1.00	19.86	A	C
ATOM	1514	CD1	TYR	A	209	72.533	19.168	25.435	1.00	19.09	A	C
ATOM	1515	CE1	TYR	A	209	72.997	18.142	26.247	1.00	20.71	A	C

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ATOM	1516	CD2	TYR	A	209	70.475	19.232	26.662	1.00	18.33	A	C
ATOM	1517	CE2	TYR	A	209	70.927	18.201	27.484	1.00	20.46	A	C
ATOM	1518	CZ	TYR	A	209	72.185	17.659	27.270	1.00	22.30	A	C
ATOM	1519	OH	TYR	A	209	72.619	16.618	28.049	1.00	25.22	A	O
ATOM	1520	C	TYR	A	209	69.625	19.153	23.227	1.00	20.01	A	C
ATOM	1521	O	TYR	A	209	68.426	19.329	23.465	1.00	18.91	A	O
ATOM	1522	N	GLY	A	210	70.141	17.961	22.940	1.00	18.48	A	N
ATOM	1523	CA	GLY	A	210	69.287	16.790	22.842	1.00	22.41	A	C
ATOM	1524	C	GLY	A	210	69.450	15.741	23.918	1.00	22.71	A	C
ATOM	1525	O	GLY	A	210	69.101	14.585	23.709	1.00	22.58	A	O
ATOM	1526	N	GLY	A	211	70.001	16.138	25.062	1.00	24.79	A	N
ATOM	1527	CA	GLY	A	211	70.177	15.209	26.167	1.00	26.36	A	C
ATOM	1528	C	GLY	A	211	68.929	15.236	27.029	1.00	27.13	A	C
ATOM	1529	O	GLY	A	211	67.875	15.663	26.556	1.00	26.25	A	O
ATOM	1530	N	SER	A	212	69.030	14.777	28.278	1.00	27.69	A	N
ATOM	1531	CA	SER	A	212	67.883	14.774	29.186	1.00	29.84	A	C
ATOM	1532	CB	SER	A	212	68.233	14.098	30.511	1.00	29.31	A	C
ATOM	1533	OG	SER	A	212	68.637	12.756	30.327	1.00	33.66	A	O
ATOM	1534	C	SER	A	212	67.450	16.206	29.484	1.00	30.00	A	C
ATOM	1535	O	SER	A	212	68.259	17.018	29.923	1.00	28.67	A	O
ATOM	1536	N	VAL	A	213	66.182	16.515	29.239	1.00	30.24	A	N
ATOM	1537	CA	VAL	A	213	65.671	17.853	29.513	1.00	30.55	A	C
ATOM	1538	CB	VAL	A	213	65.441	18.671	28.218	1.00	31.41	A	C
ATOM	1539	CG1	VAL	A	213	64.905	20.064	28.574	1.00	31.49	A	C
ATOM	1540	CG2	VAL	A	213	66.741	18.795	27.425	1.00	31.44	A	C
ATOM	1541	C	VAL	A	213	64.336	17.767	30.224	1.00	30.96	A	C
ATOM	1542	O	VAL	A	213	63.386	17.201	29.687	1.00	32.12	A	O
ATOM	1543	N	LYS	A	214	64.264	18.321	31.432	1.00	30.80	A	N
ATOM	1544	CA	LYS	A	214	63.015	18.344	32.186	1.00	30.16	A	C
ATOM	1545	CB	LYS	A	214	63.066	17.379	33.375	1.00	31.65	A	C
ATOM	1546	CG	LYS	A	214	64.219	17.592	34.327	1.00	33.28	A	C
ATOM	1547	CD	LYS	A	214	64.217	16.527	35.417	1.00	35.88	A	C
ATOM	1548	CE	LYS	A	214	64.333	15.135	34.812	1.00	38.58	A	C
ATOM	1549	NZ	LYS	A	214	64.467	14.061	35.851	1.00	40.77	A	N
ATOM	1550	C	LYS	A	214	62.712	19.763	32.661	1.00	29.23	A	C
ATOM	1551	O	LYS	A	214	63.548	20.664	32.542	1.00	27.70	A	O
ATOM	1552	N	ALA	A	215	61.509	19.957	33.191	1.00	28.62	A	N
ATOM	1553	CA	ALA	A	215	61.071	21.269	33.658	1.00	28.86	A	C
ATOM	1554	CB	ALA	A	215	59.722	21.149	34.360	1.00	27.98	A	C
ATOM	1555	C	ALA	A	215	62.073	21.931	34.588	1.00	27.64	A	C
ATOM	1556	O	ALA	A	215	62.409	23.102	34.424	1.00	28.09	A	O
ATOM	1557	N	ALA	A	216	62.559	21.173	35.558	1.00	27.89	A	N
ATOM	1558	CA	ALA	A	216	63.497	21.702	36.542	1.00	28.54	A	C
ATOM	1559	CB	ALA	A	216	63.490	20.803	37.779	1.00	28.46	A	C
ATOM	1560	C	ALA	A	216	64.938	21.924	36.079	1.00	27.78	A	C
ATOM	1561	O	ALA	A	216	65.715	22.564	36.785	1.00	27.58	A	O
ATOM	1562	N	SER	A	217	65.297	21.418	34.901	1.00	28.01	A	N
ATOM	1563	CA	SER	A	217	66.671	21.561	34.409	1.00	27.38	A	C
ATOM	1564	CB	SER	A	217	67.261	20.182	34.108	1.00	26.95	A	C
ATOM	1565	OG	SER	A	217	66.542	19.561	33.054	1.00	24.95	A	O
ATOM	1566	C	SER	A	217	66.808	22.409	33.156	1.00	27.32	A	C
ATOM	1567	O	SER	A	217	67.902	22.876	32.835	1.00	26.32	A	O
ATOM	1568	N	ALA	A	218	65.694	22.603	32.456	1.00	26.76	A	N
ATOM	1569	CA	ALA	A	218	65.680	23.355	31.206	1.00	25.53	A	C
ATOM	1570	CB	ALA	A	218	64.255	23.415	30.659	1.00	25.02	A	C
ATOM	1571	C	ALA	A	218	66.274	24.760	31.258	1.00	25.94	A	C
ATOM	1572	O	ALA	A	218	67.049	25.136	30.381	1.00	26.29	A	O
ATOM	1573	N	ALA	A	219	65.922	25.529	32.279	1.00	24.83	A	N
ATOM	1574	CA	ALA	A	219	66.408	26.902	32.384	1.00	25.74	A	C
ATOM	1575	CB	ALA	A	219	65.843	27.552	33.638	1.00	25.62	A	C
ATOM	1576	C	ALA	A	219	67.928	27.057	32.354	1.00	25.11	A	C
ATOM	1577	O	ALA	A	219	68.453	27.873	31.597	1.00	24.31	A	O
ATOM	1578	N	GLU	A	220	68.619	26.278	33.185	1.00	26.90	A	N
ATOM	1579	CA	GLU	A	220	70.078	26.313	33.294	1.00	26.66	A	C
ATOM	1580	CB	GLU	A	220	70.524	25.369	34.426	1.00	29.38	A	C
ATOM	1581	CG	GLU	A	220	72.030	25.071	34.528	1.00	32.92	A	C

FIGURE 9 - 24

ATOM	1582	CD	GLU	A	220	72.407	24.398	35.863	1.00	36.72	A	C
ATOM	1583	OE1	GLU	A	220	71.632	23.545	36.357	1.00	39.37	A	O
ATOM	1584	OE2	GLU	A	220	73.484	24.708	36.424	1.00	37.71	A	O
ATOM	1585	C	GLU	A	220	70.739	25.930	31.975	1.00	27.18	A	C
ATOM	1586	O	GLU	A	220	71.684	26.580	31.524	1.00	27.22	A	O
ATOM	1587	N	LEU	A	221	70.237	24.872	31.354	1.00	26.04	A	N
ATOM	1588	CA	LEU	A	221	70.781	24.421	30.087	1.00	25.54	A	C
ATOM	1589	CB	LEU	A	221	70.154	23.072	29.711	1.00	25.36	A	C
ATOM	1590	CG	LEU	A	221	70.814	21.831	30.323	1.00	24.33	A	C
ATOM	1591	CD1	LEU	A	221	69.912	20.623	30.183	1.00	25.52	A	C
ATOM	1592	CD2	LEU	A	221	72.152	21.585	29.635	1.00	23.47	A	C
ATOM	1593	C	LEU	A	221	70.561	25.454	28.971	1.00	24.88	A	C
ATOM	1594	O	LEU	A	221	71.508	25.868	28.303	1.00	22.01	A	O
ATOM	1595	N	PHE	A	222	69.311	25.874	28.784	1.00	25.62	A	N
ATOM	1596	CA	PHE	A	222	68.977	26.839	27.743	1.00	25.16	A	C
ATOM	1597	CB	PHE	A	222	67.467	27.086	27.702	1.00	23.47	A	C
ATOM	1598	CG	PHE	A	222	66.649	25.868	27.342	1.00	22.39	A	C
ATOM	1599	CD1	PHE	A	222	67.229	24.781	26.690	1.00	20.09	A	C
ATOM	1600	CD2	PHE	A	222	65.278	25.832	27.616	1.00	21.71	A	C
ATOM	1601	CE1	PHE	A	222	66.459	23.676	26.314	1.00	20.60	A	C
ATOM	1602	CE2	PHE	A	222	64.496	24.732	27.245	1.00	21.98	A	C
ATOM	1603	CZ	PHE	A	222	65.089	23.650	26.591	1.00	20.28	A	C
ATOM	1604	C	PHE	A	222	69.699	28.159	27.965	1.00	26.92	A	C
ATOM	1605	O	PHE	A	222	69.901	28.940	27.026	1.00	26.76	A	O
ATOM	1606	N	GLY	A	223	70.093	28.396	29.210	1.00	26.78	A	N
ATOM	1607	CA	GLY	A	223	70.783	29.624	29.544	1.00	27.48	A	C
ATOM	1608	C	GLY	A	223	72.214	29.674	29.043	1.00	27.70	A	C
ATOM	1609	O	GLY	A	223	72.808	30.744	28.951	1.00	28.93	A	O
ATOM	1610	N	MET	A	224	72.795	28.528	28.724	1.00	27.35	A	N
ATOM	1611	CA	MET	A	224	74.163	28.551	28.241	1.00	26.38	A	C
ATOM	1612	CB	MET	A	224	74.683	27.125	28.087	1.00	26.05	A	C
ATOM	1613	CG	MET	A	224	75.971	26.877	28.870	1.00	28.39	A	C
ATOM	1614	SD	MET	A	224	75.806	27.008	30.649	1.00	24.91	A	S
ATOM	1615	CE	MET	A	224	77.257	26.125	31.131	1.00	27.81	A	C
ATOM	1616	C	MET	A	224	74.241	29.334	26.913	1.00	25.44	A	C
ATOM	1617	O	MET	A	224	73.301	29.337	26.117	1.00	24.05	A	O
ATOM	1618	N	PRO	A	225	75.366	30.024	26.673	1.00	26.30	A	N
ATOM	1619	CD	PRO	A	225	76.582	30.042	27.504	1.00	27.39	A	C
ATOM	1620	CA	PRO	A	225	75.564	30.817	25.456	1.00	26.61	A	C
ATOM	1621	CB	PRO	A	225	76.982	31.361	25.625	1.00	28.19	A	C
ATOM	1622	CG	PRO	A	225	77.652	30.322	26.484	1.00	28.50	A	C
ATOM	1623	C	PRO	A	225	75.365	30.129	24.099	1.00	25.97	A	C
ATOM	1624	O	PRO	A	225	74.741	30.694	23.209	1.00	25.42	A	O
ATOM	1625	N	ASP	A	226	75.876	28.918	23.932	1.00	25.30	A	N
ATOM	1626	CA	ASP	A	226	75.733	28.256	22.641	1.00	26.40	A	C
ATOM	1627	CB	ASP	A	226	77.083	27.657	22.232	1.00	25.52	A	C
ATOM	1628	CG	ASP	A	226	78.132	28.732	21.956	1.00	28.90	A	C
ATOM	1629	OD1	ASP	A	226	78.042	29.393	20.897	1.00	29.10	A	O
ATOM	1630	OD2	ASP	A	226	79.038	28.926	22.803	1.00	29.86	A	O
ATOM	1631	C	ASP	A	226	74.603	27.218	22.531	1.00	25.89	A	C
ATOM	1632	O	ASP	A	226	74.570	26.416	21.595	1.00	23.67	A	O
ATOM	1633	N	ILE	A	227	73.675	27.249	23.484	1.00	24.91	A	N
ATOM	1634	CA	ILE	A	227	72.537	26.336	23.466	1.00	26.34	A	C
ATOM	1635	CB	ILE	A	227	72.366	25.623	24.813	1.00	27.46	A	C
ATOM	1636	CG2	ILE	A	227	71.213	24.623	24.723	1.00	26.87	A	C
ATOM	1637	CG1	ILE	A	227	73.669	24.913	25.190	1.00	27.28	A	C
ATOM	1638	CD1	ILE	A	227	73.574	24.071	26.453	1.00	27.14	A	C
ATOM	1639	C	ILE	A	227	71.287	27.154	23.154	1.00	25.41	A	C
ATOM	1640	O	ILE	A	227	70.873	27.999	23.939	1.00	27.14	A	O
ATOM	1641	N	ASP	A	228	70.685	26.893	22.003	1.00	25.95	A	N
ATOM	1642	CA	ASP	A	228	69.524	27.651	21.562	1.00	25.76	A	C
ATOM	1643	CB	ASP	A	228	69.687	27.963	20.076	1.00	24.22	A	C
ATOM	1644	CG	ASP	A	228	71.015	28.639	19.776	1.00	27.22	A	C
ATOM	1645	OD1	ASP	A	228	71.770	28.127	18.914	1.00	27.25	A	O
ATOM	1646	OD2	ASP	A	228	71.302	29.681	20.413	1.00	26.31	A	O
ATOM	1647	C	ASP	A	228	68.160	27.020	21.818	1.00	25.91	A	C

FIGURE 9 - 25

ATOM	1648	O	ASP	A	228	67.149	27.471	21.273	1.00	27.55	A	O
ATOM	1649	N	GLY	A	229	68.128	25.995	22.659	1.00	24.49	A	N
ATOM	1650	CA	GLY	A	229	66.876	25.335	22.962	1.00	24.44	A	C
ATOM	1651	C	GLY	A	229	67.110	23.852	23.149	1.00	24.31	A	C
ATOM	1652	O	GLY	A	229	68.244	23.419	23.375	1.00	24.14	A	O
ATOM	1653	N	GLY	A	230	66.048	23.063	23.063	1.00	22.84	A	N
ATOM	1654	CA	GLY	A	230	66.213	21.636	23.236	1.00	22.20	A	C
ATOM	1655	C	GLY	A	230	65.335	20.759	22.360	1.00	23.21	A	C
ATOM	1656	O	GLY	A	230	64.293	21.190	21.843	1.00	22.77	A	O
ATOM	1657	N	LEU	A	231	65.789	19.525	22.173	1.00	21.78	A	N
ATOM	1658	CA	LEU	A	231	65.058	18.533	21.407	1.00	22.79	A	C
ATOM	1659	CB	LEU	A	231	65.972	17.837	20.394	1.00	20.20	A	C
ATOM	1660	CG	LEU	A	231	65.335	16.753	19.513	1.00	16.73	A	C
ATOM	1661	CD1	LEU	A	231	64.094	17.277	18.822	1.00	16.37	A	C
ATOM	1662	CD2	LEU	A	231	66.353	16.285	18.498	1.00	16.99	A	C
ATOM	1663	C	LEU	A	231	64.647	17.582	22.515	1.00	22.71	A	C
ATOM	1664	O	LEU	A	231	65.340	16.619	22.813	1.00	24.85	A	O
ATOM	1665	N	VAL	A	232	63.516	17.898	23.130	1.00	23.84	A	N
ATOM	1666	CA	VAL	A	232	62.967	17.165	24.263	1.00	23.85	A	C
ATOM	1667	CB	VAL	A	232	61.820	17.972	24.892	1.00	24.09	A	C
ATOM	1668	CG1	VAL	A	232	61.448	17.394	26.255	1.00	23.17	A	C
ATOM	1669	CG2	VAL	A	232	62.222	19.431	24.987	1.00	21.20	A	C
ATOM	1670	C	VAL	A	232	62.447	15.777	23.927	1.00	25.57	A	C
ATOM	1671	O	VAL	A	232	61.821	15.576	22.887	1.00	25.74	A	O
ATOM	1672	N	GLY	A	233	62.692	14.828	24.829	1.00	26.04	A	N
ATOM	1673	CA	GLY	A	233	62.240	13.461	24.619	1.00	26.94	A	C
ATOM	1674	C	GLY	A	233	60.923	13.174	25.315	1.00	25.88	A	C
ATOM	1675	O	GLY	A	233	59.947	13.896	25.129	1.00	27.25	A	O
ATOM	1676	N	GLY	A	234	60.911	12.127	26.136	1.00	24.68	A	N
ATOM	1677	CA	GLY	A	234	59.709	11.734	26.852	1.00	23.13	A	C
ATOM	1678	C	GLY	A	234	58.901	12.858	27.480	1.00	22.51	A	C
ATOM	1679	O	GLY	A	234	57.669	12.808	27.483	1.00	21.53	A	O
ATOM	1680	N	ALA	A	235	59.587	13.864	28.016	1.00	20.33	A	N
ATOM	1681	CA	ALA	A	235	58.913	14.982	28.658	1.00	20.17	A	C
ATOM	1682	CB	ALA	A	235	59.937	15.975	29.209	1.00	21.87	A	C
ATOM	1683	C	ALA	A	235	57.968	15.685	27.696	1.00	20.55	A	C
ATOM	1684	O	ALA	A	235	57.055	16.380	28.133	1.00	21.17	A	O
ATOM	1685	N	SER	A	236	58.179	15.511	26.392	1.00	19.15	A	N
ATOM	1686	CA	SER	A	236	57.303	16.151	25.423	1.00	19.11	A	C
ATOM	1687	CB	SER	A	236	57.986	16.276	24.061	1.00	18.61	A	C
ATOM	1688	OG	SER	A	236	58.023	15.044	23.371	1.00	22.28	A	O
ATOM	1689	C	SER	A	236	55.993	15.373	25.285	1.00	20.21	A	C
ATOM	1690	O	SER	A	236	55.124	15.745	24.496	1.00	19.31	A	O
ATOM	1691	N	LEU	A	237	55.861	14.300	26.064	1.00	19.77	A	N
ATOM	1692	CA	LEU	A	237	54.657	13.470	26.063	1.00	21.74	A	C
ATOM	1693	CB	LEU	A	237	55.011	12.018	26.401	1.00	21.73	A	C
ATOM	1694	CG	LEU	A	237	55.272	11.064	25.227	1.00	24.24	A	C
ATOM	1695	CD1	LEU	A	237	55.669	11.841	23.980	1.00	24.31	A	C
ATOM	1696	CD2	LEU	A	237	56.354	10.064	25.620	1.00	23.37	A	C
ATOM	1697	C	LEU	A	237	53.591	13.977	27.034	1.00	21.75	A	C
ATOM	1698	O	LEU	A	237	52.479	13.461	27.060	1.00	22.31	A	O
ATOM	1699	N	ASN	A	238	53.939	14.972	27.844	1.00	22.17	A	N
ATOM	1700	CA	ASN	A	238	52.997	15.557	28.796	1.00	22.68	A	C
ATOM	1701	CB	ASN	A	238	53.491	15.358	30.234	1.00	21.33	A	C
ATOM	1702	CG	ASN	A	238	52.523	15.910	31.270	1.00	22.65	A	C
ATOM	1703	OD1	ASN	A	238	52.555	17.091	31.596	1.00	22.15	A	O
ATOM	1704	ND2	ASN	A	238	51.649	15.051	31.782	1.00	21.80	A	N
ATOM	1705	C	ASN	A	238	52.875	17.045	28.466	1.00	22.64	A	C
ATOM	1706	O	ASN	A	238	53.860	17.779	28.513	1.00	22.21	A	O
ATOM	1707	N	ALA	A	239	51.662	17.481	28.130	1.00	23.15	A	N
ATOM	1708	CA	ALA	A	239	51.422	18.869	27.745	1.00	23.18	A	C
ATOM	1709	CB	ALA	A	239	49.920	19.127	27.590	1.00	24.02	A	C
ATOM	1710	C	ALA	A	239	52.025	19.905	28.674	1.00	22.58	A	C
ATOM	1711	O	ALA	A	239	52.894	20.671	28.261	1.00	21.87	A	O
ATOM	1712	N	ASP	A	240	51.569	19.935	29.924	1.00	23.40	A	N
ATOM	1713	CA	ASP	A	240	52.065	20.924	30.885	1.00	24.99	A	C

FIGURE 9 - 26

ATOM	1714	CB	ASP	A	240	51.301	20.820	32.218	1.00	28.18	A	C
ATOM	1715	CG	ASP	A	240	49.787	21.046	32.058	1.00	34.40	A	C
ATOM	1716	OD1	ASP	A	240	49.375	21.956	31.294	1.00	34.40	A	O
ATOM	1717	OD2	ASP	A	240	49.003	20.319	32.710	1.00	35.74	A	O
ATOM	1718	C	ASP	A	240	53.583	20.873	31.139	1.00	23.24	A	C
ATOM	1719	O	ASP	A	240	54.215	21.914	31.296	1.00	22.53	A	O
ATOM	1720	N	GLU	A	241	54.168	19.676	31.172	1.00	22.93	A	N
ATOM	1721	CA	GLU	A	241	55.610	19.558	31.399	1.00	23.44	A	C
ATOM	1722	CB	GLU	A	241	56.019	18.087	31.594	1.00	23.75	A	C
ATOM	1723	CG	GLU	A	241	57.496	17.884	31.983	1.00	23.96	A	C
ATOM	1724	CD	GLU	A	241	57.846	16.428	32.310	1.00	25.18	A	C
ATOM	1725	OE1	GLU	A	241	57.309	15.511	31.658	1.00	24.74	A	O
ATOM	1726	OE2	GLU	A	241	58.673	16.197	33.211	1.00	26.97	A	O
ATOM	1727	C	GLU	A	241	56.362	20.162	30.209	1.00	21.74	A	C
ATOM	1728	O	GLU	A	241	57.387	20.813	30.382	1.00	21.93	A	O
ATOM	1729	N	PHE	A	242	55.846	19.935	29.005	1.00	21.24	A	N
ATOM	1730	CA	PHE	A	242	56.457	20.468	27.791	1.00	20.79	A	C
ATOM	1731	CB	PHE	A	242	55.753	19.906	26.554	1.00	18.97	A	C
ATOM	1732	CG	PHE	A	242	56.376	20.329	25.258	1.00	16.57	A	C
ATOM	1733	CD1	PHE	A	242	57.694	20.003	24.966	1.00	17.22	A	C
ATOM	1734	CD2	PHE	A	242	55.645	21.055	24.325	1.00	17.37	A	C
ATOM	1735	CE1	PHE	A	242	58.267	20.389	23.776	1.00	12.97	A	C
ATOM	1736	CE2	PHE	A	242	56.214	21.446	23.130	1.00	14.33	A	C
ATOM	1737	CZ	PHE	A	242	57.529	21.111	22.857	1.00	16.37	A	C
ATOM	1738	C	PHE	A	242	56.339	21.990	27.797	1.00	21.03	A	C
ATOM	1739	O	PHE	A	242	57.229	22.697	27.332	1.00	21.95	A	O
ATOM	1740	N	GLY	A	243	55.228	22.484	28.330	1.00	20.92	A	N
ATOM	1741	CA	GLY	A	243	55.015	23.915	28.401	1.00	19.75	A	C
ATOM	1742	C	GLY	A	243	56.014	24.589	29.324	1.00	20.31	A	C
ATOM	1743	O	GLY	A	243	56.532	25.667	29.025	1.00	18.71	A	O
ATOM	1744	N	ALA	A	244	56.295	23.953	30.455	1.00	20.28	A	N
ATOM	1745	CA	ALA	A	244	57.242	24.521	31.400	1.00	22.47	A	C
ATOM	1746	CB	ALA	A	244	57.265	23.700	32.674	1.00	22.84	A	C
ATOM	1747	C	ALA	A	244	58.636	24.588	30.785	1.00	23.43	A	C
ATOM	1748	O	ALA	A	244	59.420	25.479	31.107	1.00	24.58	A	O
ATOM	1749	N	ILE	A	245	58.950	23.650	29.895	1.00	24.41	A	N
ATOM	1750	CA	ILE	A	245	60.269	23.645	29.259	1.00	23.65	A	C
ATOM	1751	CB	ILE	A	245	60.573	22.282	28.618	1.00	22.77	A	C
ATOM	1752	CG2	ILE	A	245	61.906	22.337	27.880	1.00	23.46	A	C
ATOM	1753	CG1	ILE	A	245	60.580	21.206	29.709	1.00	23.75	A	C
ATOM	1754	CD1	ILE	A	245	60.959	19.830	29.235	1.00	24.48	A	C
ATOM	1755	C	ILE	A	245	60.374	24.749	28.207	1.00	23.26	A	C
ATOM	1756	O	ILE	A	245	61.423	25.379	28.069	1.00	22.75	A	O
ATOM	1757	N	CYS	A	246	59.289	24.977	27.469	1.00	22.68	A	N
ATOM	1758	CA	CYS	A	246	59.269	26.029	26.458	1.00	24.31	A	C
ATOM	1759	CB	CYS	A	246	57.934	26.042	25.707	1.00	23.73	A	C
ATOM	1760	SG	CYS	A	246	57.624	24.624	24.638	1.00	24.50	A	S
ATOM	1761	C	CYS	A	246	59.446	27.368	27.166	1.00	24.44	A	C
ATOM	1762	O	CYS	A	246	60.242	28.213	26.757	1.00	26.55	A	O
ATOM	1763	N	ARG	A	247	58.695	27.549	28.241	1.00	24.08	A	N
ATOM	1764	CA	ARG	A	247	58.750	28.787	29.003	1.00	26.08	A	C
ATOM	1765	CB	ARG	A	247	57.763	28.704	30.171	1.00	27.21	A	C
ATOM	1766	CG	ARG	A	247	57.135	30.025	30.564	1.00	30.39	A	C
ATOM	1767	CD	ARG	A	247	55.931	29.800	31.467	1.00	31.58	A	C
ATOM	1768	NE	ARG	A	247	54.775	29.253	30.747	1.00	30.93	A	N
ATOM	1769	CZ	ARG	A	247	54.268	28.035	30.940	1.00	30.00	A	C
ATOM	1770	NH1	ARG	A	247	54.815	27.211	31.832	1.00	27.30	A	N
ATOM	1771	NH2	ARG	A	247	53.183	27.653	30.262	1.00	29.94	A	N
ATOM	1772	C	ARG	A	247	60.170	29.048	29.506	1.00	25.08	A	C
ATOM	1773	O	ARG	A	247	60.642	30.183	29.495	1.00	24.80	A	O
ATOM	1774	N	ALA	A	248	60.854	27.988	29.926	1.00	26.03	A	N
ATOM	1775	CA	ALA	A	248	62.221	28.107	30.427	1.00	25.39	A	C
ATOM	1776	CB	ALA	A	248	62.715	26.756	30.914	1.00	26.95	A	C
ATOM	1777	C	ALA	A	248	63.167	28.649	29.365	1.00	25.92	A	C
ATOM	1778	O	ALA	A	248	64.271	29.085	29.667	1.00	26.97	A	O
ATOM	1779	N	ALA	A	249	62.738	28.620	28.113	1.00	27.25	A	N

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ATOM	1780	CA	ALA	A	249	63.579	29.121	27.035	1.00	28.40	A	C
ATOM	1781	CB	ALA	A	249	63.377	28.274	25.791	1.00	26.39	A	C
ATOM	1782	C	ALA	A	249	63.301	30.592	26.714	1.00	29.71	A	C
ATOM	1783	O	ALA	A	249	64.059	31.209	25.971	1.00	30.25	A	O
ATOM	1784	N	GLY	A	250	62.224	31.146	27.271	1.00	32.16	A	N
ATOM	1785	CA	GLY	A	250	61.873	32.535	26.999	1.00	36.17	A	C
ATOM	1786	C	GLY	A	250	62.337	33.560	28.022	1.00	39.60	A	C
ATOM	1787	O	GLY	A	250	63.221	34.399	27.693	1.00	41.59	A	O
ATOM	1788	OXT	GLY	A	250	61.822	33.535	29.161	1.00	42.10	A	O
TER	1789		GLY	A	250						A	
ATOM	1790	CB	MET	B	1	38.254	-23.711	-0.133	1.00	39.29	B	C
ATOM	1791	CG	MET	B	1	37.707	-24.999	-0.760	1.00	41.51	B	C
ATOM	1792	SD	MET	B	1	38.988	-25.999	-1.568	1.00	43.23	B	S
ATOM	1793	CE	MET	B	1	38.759	-27.639	-0.702	1.00	41.88	B	C
ATOM	1794	C	MET	B	1	40.027	-22.521	1.143	1.00	38.04	B	C
ATOM	1795	O	MET	B	1	39.397	-21.686	1.796	1.00	37.73	B	O
ATOM	1796	N	MET	B	1	38.926	-24.565	2.117	1.00	37.65	B	N
ATOM	1797	CA	MET	B	1	39.412	-23.895	0.860	1.00	38.46	B	C
ATOM	1798	N	ARG	B	2	41.245	-22.286	0.648	1.00	36.65	B	N
ATOM	1799	CA	ARG	B	2	41.916	-20.996	0.855	1.00	34.99	B	C
ATOM	1800	CB	ARG	B	2	43.265	-20.940	0.127	1.00	34.38	B	C
ATOM	1801	CG	ARG	B	2	44.359	-21.824	0.705	1.00	33.70	B	C
ATOM	1802	CD	ARG	B	2	45.687	-21.565	-0.003	1.00	30.29	B	C
ATOM	1803	NE	ARG	B	2	45.641	-21.950	-1.413	1.00	28.14	B	N
ATOM	1804	CZ	ARG	B	2	45.937	-23.163	-1.873	1.00	29.01	B	C
ATOM	1805	NH1	ARG	B	2	46.312	-24.116	-1.038	1.00	26.43	B	N
ATOM	1806	NH2	ARG	B	2	45.844	-23.432	-3.174	1.00	29.39	B	N
ATOM	1807	C	ARG	B	2	41.038	-19.883	0.311	1.00	33.64	B	C
ATOM	1808	O	ARG	B	2	40.539	-19.969	-0.810	1.00	34.35	B	O
ATOM	1809	N	ARG	B	3	40.864	-18.830	1.095	1.00	32.19	B	N
ATOM	1810	CA	ARG	B	3	40.038	-17.705	0.676	1.00	29.95	B	C
ATOM	1811	CB	ARG	B	3	39.452	-17.055	1.927	1.00	30.86	B	C
ATOM	1812	CG	ARG	B	3	38.335	-16.067	1.698	1.00	32.31	B	C
ATOM	1813	CD	ARG	B	3	37.760	-15.587	3.041	1.00	33.83	B	C
ATOM	1814	NE	ARG	B	3	36.913	-14.410	2.856	1.00	35.04	B	N
ATOM	1815	CZ	ARG	B	3	35.695	-14.438	2.328	1.00	35.89	B	C
ATOM	1816	NH1	ARG	B	3	35.166	-15.593	1.941	1.00	36.43	B	N
ATOM	1817	NH2	ARG	B	3	35.018	-13.305	2.158	1.00	36.37	B	N
ATOM	1818	C	ARG	B	3	40.888	-16.708	-0.121	1.00	29.77	B	C
ATOM	1819	O	ARG	B	3	41.971	-16.327	0.316	1.00	30.29	B	O
ATOM	1820	N	PRO	B	4	40.423	-16.284	-1.313	1.00	29.13	B	N
ATOM	1821	CD	PRO	B	4	39.280	-16.795	-2.090	1.00	29.44	B	C
ATOM	1822	CA	PRO	B	4	41.204	-15.327	-2.112	1.00	28.31	B	C
ATOM	1823	CB	PRO	B	4	40.353	-15.155	-3.368	1.00	29.26	B	C
ATOM	1824	CG	PRO	B	4	39.702	-16.496	-3.517	1.00	29.38	B	C
ATOM	1825	C	PRO	B	4	41.465	-13.986	-1.402	1.00	29.09	B	C
ATOM	1826	O	PRO	B	4	40.630	-13.503	-0.626	1.00	26.82	B	O
ATOM	1827	N	LEU	B	5	42.621	-13.386	-1.688	1.00	27.53	B	N
ATOM	1828	CA	LEU	B	5	43.001	-12.107	-1.085	1.00	26.45	B	C
ATOM	1829	CB	LEU	B	5	44.046	-12.316	0.018	1.00	25.53	B	C
ATOM	1830	CG	LEU	B	5	44.799	-11.068	0.510	1.00	24.95	B	C
ATOM	1831	CD1	LEU	B	5	43.837	-10.111	1.177	1.00	25.86	B	C
ATOM	1832	CD2	LEU	B	5	45.893	-11.466	1.482	1.00	23.55	B	C
ATOM	1833	C	LEU	B	5	43.572	-11.153	-2.120	1.00	26.71	B	C
ATOM	1834	O	LEU	B	5	44.498	-11.497	-2.854	1.00	27.09	B	O
ATOM	1835	N	VAL	B	6	43.015	-9.950	-2.178	1.00	26.99	B	N
ATOM	1836	CA	VAL	B	6	43.495	-8.939	-3.106	1.00	27.35	B	C
ATOM	1837	CB	VAL	B	6	42.406	-8.533	-4.101	1.00	27.88	B	C
ATOM	1838	CG1	VAL	B	6	42.920	-7.413	-4.999	1.00	26.82	B	C
ATOM	1839	CG2	VAL	B	6	41.987	-9.749	-4.920	1.00	28.26	B	C
ATOM	1840	C	VAL	B	6	43.898	-7.727	-2.283	1.00	28.26	B	C
ATOM	1841	O	VAL	B	6	43.043	-7.045	-1.721	1.00	30.19	B	O
ATOM	1842	N	ALA	B	7	45.199	-7.461	-2.209	1.00	28.32	B	N
ATOM	1843	CA	ALA	B	7	45.709	-6.341	-1.422	1.00	27.60	B	C
ATOM	1844	CB	ALA	B	7	46.636	-6.863	-0.348	1.00	27.24	B	C
ATOM	1845	C	ALA	B	7	46.432	-5.305	-2.279	1.00	27.32	B	C

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ATOM	1846	O	ALA	B	7	47.255	-5.644	-3.130	1.00	27.65	B	O
ATOM	1847	N	GLY	B	8	46.130	-4.036	-2.029	1.00	26.92	B	N
ATOM	1848	CA	GLY	B	8	46.737	-2.965	-2.797	1.00	26.72	B	C
ATOM	1849	C	GLY	B	8	47.813	-2.189	-2.062	1.00	26.89	B	C
ATOM	1850	O	GLY	B	8	47.592	-1.667	-0.972	1.00	26.02	B	O
ATOM	1851	N	ASN	B	9	48.991	-2.120	-2.670	1.00	26.08	B	N
ATOM	1852	CA	ASN	B	9	50.115	-1.403	-2.094	1.00	24.90	B	C
ATOM	1853	CB	ASN	B	9	51.409	-2.180	-2.313	1.00	23.23	B	C
ATOM	1854	CG	ASN	B	9	52.612	-1.445	-1.788	1.00	21.91	B	C
ATOM	1855	OD1	ASN	B	9	52.478	-0.526	-0.989	1.00	22.31	B	O
ATOM	1856	ND2	ASN	B	9	53.799	-1.851	-2.222	1.00	19.96	B	N
ATOM	1857	C	ASN	B	9	50.211	-0.045	-2.766	1.00	23.88	B	C
ATOM	1858	O	ASN	B	9	50.701	0.066	-3.883	1.00	23.71	B	O
ATOM	1859	N	TRP	B	10	49.738	0.983	-2.075	1.00	23.64	B	N
ATOM	1860	CA	TRP	B	10	49.748	2.335	-2.611	1.00	23.50	B	C
ATOM	1861	CB	TRP	B	10	48.905	3.257	-1.719	1.00	24.27	B	C
ATOM	1862	CG	TRP	B	10	47.450	2.907	-1.635	1.00	23.37	B	C
ATOM	1863	CD2	TRP	B	10	46.424	3.663	-0.973	1.00	25.18	B	C
ATOM	1864	CE2	TRP	B	10	45.212	2.950	-1.123	1.00	23.26	B	C
ATOM	1865	CE3	TRP	B	10	46.412	4.874	-0.266	1.00	23.36	B	C
ATOM	1866	CD1	TRP	B	10	46.833	1.796	-2.149	1.00	25.60	B	C
ATOM	1867	NE1	TRP	B	10	45.486	1.816	-1.844	1.00	24.60	B	N
ATOM	1868	CZ2	TRP	B	10	44.001	3.410	-0.588	1.00	24.13	B	C
ATOM	1869	CZ3	TRP	B	10	45.207	5.329	0.265	1.00	22.31	B	C
ATOM	1870	CH2	TRP	B	10	44.022	4.597	0.100	1.00	23.37	B	C
ATOM	1871	C	TRP	B	10	51.158	2.901	-2.720	1.00	23.33	B	C
ATOM	1872	O	TRP	B	10	51.393	3.859	-3.459	1.00	26.44	B	O
ATOM	1873	N	LYS	B	11	52.090	2.301	-1.989	1.00	22.51	B	N
ATOM	1874	CA	LYS	B	11	53.476	2.763	-1.961	1.00	24.92	B	C
ATOM	1875	CB	LYS	B	11	54.137	2.588	-3.336	1.00	24.05	B	C
ATOM	1876	CG	LYS	B	11	54.235	1.115	-3.764	1.00	22.53	B	C
ATOM	1877	CD	LYS	B	11	55.080	0.916	-5.023	1.00	23.18	B	C
ATOM	1878	CE	LYS	B	11	55.147	-0.561	-5.391	1.00	23.09	B	C
ATOM	1879	NZ	LYS	B	11	56.049	-0.856	-6.533	1.00	24.44	B	N
ATOM	1880	C	LYS	B	11	53.570	4.220	-1.468	1.00	24.17	B	C
ATOM	1881	O	LYS	B	11	52.679	4.684	-0.763	1.00	23.95	B	O
ATOM	1882	N	MET	B	12	54.637	4.931	-1.831	1.00	24.23	B	N
ATOM	1883	CA	MET	B	12	54.843	6.321	-1.376	1.00	23.99	B	C
ATOM	1884	CB	MET	B	12	56.356	6.657	-1.450	1.00	20.54	B	C
ATOM	1885	CG	MET	B	12	56.822	7.931	-0.704	1.00	17.88	B	C
ATOM	1886	SD	MET	B	12	58.635	8.096	-0.443	1.00	8.79	B	S
ATOM	1887	CE	MET	B	12	59.199	8.336	-2.054	1.00	14.14	B	C
ATOM	1888	C	MET	B	12	54.004	7.341	-2.169	1.00	22.63	B	C
ATOM	1889	O	MET	B	12	54.551	8.218	-2.829	1.00	23.70	B	O
ATOM	1890	N	HIS	B	13	52.677	7.232	-2.086	1.00	23.59	B	N
ATOM	1891	CA	HIS	B	13	51.783	8.135	-2.823	1.00	24.71	B	C
ATOM	1892	CB	HIS	B	13	51.226	7.461	-4.075	1.00	24.25	B	C
ATOM	1893	CG	HIS	B	13	52.249	7.148	-5.115	1.00	25.34	B	C
ATOM	1894	CD2	HIS	B	13	52.654	7.847	-6.200	1.00	24.96	B	C
ATOM	1895	ND1	HIS	B	13	52.959	5.966	-5.130	1.00	26.90	B	N
ATOM	1896	CE1	HIS	B	13	53.755	5.950	-6.185	1.00	27.01	B	C
ATOM	1897	NE2	HIS	B	13	53.589	7.079	-6.850	1.00	26.99	B	N
ATOM	1898	C	HIS	B	13	50.575	8.686	-2.078	1.00	25.92	B	C
ATOM	1899	O	HIS	B	13	50.131	8.131	-1.073	1.00	26.14	B	O
ATOM	1900	N	GLY	B	14	50.033	9.777	-2.616	1.00	26.76	B	N
ATOM	1901	CA	GLY	B	14	48.849	10.390	-2.048	1.00	26.86	B	C
ATOM	1902	C	GLY	B	14	48.996	11.700	-1.293	1.00	28.49	B	C
ATOM	1903	O	GLY	B	14	50.073	12.043	-0.805	1.00	28.16	B	O
ATOM	1904	N	THR	B	15	47.881	12.427	-1.231	1.00	28.51	B	N
ATOM	1905	CA	THR	B	15	47.741	13.693	-0.522	1.00	30.91	B	C
ATOM	1906	CB	THR	B	15	47.760	14.898	-1.490	1.00	31.69	B	C
ATOM	1907	OG1	THR	B	15	46.666	14.789	-2.408	1.00	33.09	B	O
ATOM	1908	CG2	THR	B	15	49.075	14.942	-2.282	1.00	31.05	B	C
ATOM	1909	C	THR	B	15	46.348	13.570	0.118	1.00	32.25	B	C
ATOM	1910	O	THR	B	15	45.609	12.649	-0.222	1.00	32.77	B	O
ATOM	1911	N	HIS	B	16	45.987	14.458	1.042	1.00	31.79	B	N

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ATOM	1912	CA	HIS	B	16	44.667	14.377	1.680	1.00	34.07	B	C
ATOM	1913	CB	HIS	B	16	44.413	15.582	2.607	1.00	36.99	B	C
ATOM	1914	CG	HIS	B	16	44.949	15.411	3.996	1.00	41.23	B	C
ATOM	1915	CD2	HIS	B	16	45.811	16.167	4.720	1.00	43.07	B	C
ATOM	1916	ND1	HIS	B	16	44.581	14.363	4.813	1.00	43.20	B	N
ATOM	1917	CE1	HIS	B	16	45.194	14.479	5.979	1.00	44.48	B	C
ATOM	1918	NE2	HIS	B	16	45.947	15.567	5.949	1.00	44.04	B	N
ATOM	1919	C	HIS	B	16	43.536	14.318	0.658	1.00	32.73	B	C
ATOM	1920	O	HIS	B	16	42.553	13.600	0.844	1.00	32.91	B	O
ATOM	1921	N	SER	B	17	43.686	15.084	-0.414	1.00	32.54	B	N
ATOM	1922	CA	SER	B	17	42.683	15.158	-1.466	1.00	33.11	B	C
ATOM	1923	CB	SER	B	17	42.908	16.407	-2.304	1.00	33.96	B	C
ATOM	1924	OG	SER	B	17	42.091	16.365	-3.456	1.00	37.21	B	O
ATOM	1925	C	SER	B	17	42.614	13.946	-2.390	1.00	32.16	B	C
ATOM	1926	O	SER	B	17	41.523	13.475	-2.696	1.00	32.55	B	O
ATOM	1927	N	SER	B	18	43.762	13.456	-2.852	1.00	30.83	B	N
ATOM	1928	CA	SER	B	18	43.782	12.286	-3.736	1.00	30.50	B	C
ATOM	1929	CB	SER	B	18	45.195	12.033	-4.273	1.00	31.03	B	C
ATOM	1930	OG	SER	B	18	46.046	11.526	-3.260	1.00	28.73	B	O
ATOM	1931	C	SER	B	18	43.298	11.035	-2.994	1.00	30.38	B	C
ATOM	1932	O	SER	B	18	42.602	10.196	-3.562	1.00	30.63	B	O
ATOM	1933	N	VAL	B	19	43.672	10.915	-1.723	1.00	29.38	B	N
ATOM	1934	CA	VAL	B	19	43.265	9.774	-0.915	1.00	29.67	B	C
ATOM	1935	CB	VAL	B	19	43.971	9.771	0.454	1.00	26.63	B	C
ATOM	1936	CG1	VAL	B	19	43.428	8.639	1.309	1.00	25.40	B	C
ATOM	1937	CG2	VAL	B	19	45.471	9.647	0.267	1.00	24.86	B	C
ATOM	1938	C	VAL	B	19	41.755	9.808	-0.674	1.00	31.95	B	C
ATOM	1939	O	VAL	B	19	41.076	8.781	-0.762	1.00	32.34	B	O
ATOM	1940	N	ALA	B	20	41.234	10.989	-0.352	1.00	33.03	B	N
ATOM	1941	CA	ALA	B	20	39.809	11.127	-0.107	1.00	35.20	B	C
ATOM	1942	CB	ALA	B	20	39.479	12.566	0.267	1.00	36.29	B	C
ATOM	1943	C	ALA	B	20	39.065	10.725	-1.374	1.00	36.05	B	C
ATOM	1944	O	ALA	B	20	37.976	10.152	-1.318	1.00	35.79	B	O
ATOM	1945	N	GLU	B	21	39.671	11.021	-2.519	1.00	37.66	B	N
ATOM	1946	CA	GLU	B	21	39.073	10.693	-3.810	1.00	39.08	B	C
ATOM	1947	CB	GLU	B	21	39.830	11.406	-4.936	1.00	42.14	B	C
ATOM	1948	CG	GLU	B	21	39.014	11.631	-6.204	1.00	47.37	B	C
ATOM	1949	CD	GLU	B	21	38.055	12.818	-6.080	1.00	51.11	B	C
ATOM	1950	OE1	GLU	B	21	38.539	13.983	-6.033	1.00	52.26	B	O
ATOM	1951	OE2	GLU	B	21	36.820	12.586	-6.028	1.00	51.43	B	O
ATOM	1952	C	GLU	B	21	39.134	9.174	-4.011	1.00	37.78	B	C
ATOM	1953	O	GLU	B	21	38.166	8.560	-4.457	1.00	37.86	B	O
ATOM	1954	N	LEU	B	22	40.267	8.567	-3.675	1.00	35.56	B	N
ATOM	1955	CA	LEU	B	22	40.400	7.126	-3.827	1.00	34.47	B	C
ATOM	1956	CB	LEU	B	22	41.842	6.680	-3.540	1.00	33.30	B	C
ATOM	1957	CG	LEU	B	22	42.174	5.213	-3.857	1.00	31.98	B	C
ATOM	1958	CD1	LEU	B	22	41.720	4.860	-5.264	1.00	29.19	B	C
ATOM	1959	CD2	LEU	B	22	43.662	4.989	-3.711	1.00	31.33	B	C
ATOM	1960	C	LEU	B	22	39.422	6.414	-2.891	1.00	34.47	B	C
ATOM	1961	O	LEU	B	22	38.770	5.446	-3.292	1.00	34.84	B	O
ATOM	1962	N	ILE	B	23	39.307	6.902	-1.656	1.00	34.19	B	N
ATOM	1963	CA	ILE	B	23	38.388	6.315	-0.678	1.00	36.16	B	C
ATOM	1964	CB	ILE	B	23	38.422	7.068	0.671	1.00	35.63	B	C
ATOM	1965	CG2	ILE	B	23	37.284	6.585	1.561	1.00	33.94	B	C
ATOM	1966	CG1	ILE	B	23	39.764	6.862	1.373	1.00	35.67	B	C
ATOM	1967	CD1	ILE	B	23	39.860	7.600	2.702	1.00	34.50	B	C
ATOM	1968	C	ILE	B	23	36.949	6.389	-1.194	1.00	37.68	B	C
ATOM	1969	O	ILE	B	23	36.133	5.503	-0.946	1.00	36.61	B	O
ATOM	1970	N	LYS	B	24	36.645	7.468	-1.900	1.00	39.87	B	N
ATOM	1971	CA	LYS	B	24	35.311	7.661	-2.439	1.00	41.28	B	C
ATOM	1972	CB	LYS	B	24	35.257	8.982	-3.210	1.00	42.72	B	C
ATOM	1973	CG	LYS	B	24	33.848	9.512	-3.451	1.00	45.01	B	C
ATOM	1974	CD	LYS	B	24	33.892	10.865	-4.142	1.00	45.93	B	C
ATOM	1975	CE	LYS	B	24	32.513	11.504	-4.199	1.00	46.92	B	C
ATOM	1976	NZ	LYS	B	24	32.587	12.873	-4.795	1.00	48.33	B	N
ATOM	1977	C	LYS	B	24	35.002	6.493	-3.367	1.00	41.36	B	C

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ATOM	1978	O	LYS	B	24	34.050	5.746	-3.138	1.00	41.22	B	O
ATOM	1979	N	GLY	B	25	35.825	6.339	-4.404	1.00	40.93	B	N
ATOM	1980	CA	GLY	B	25	35.639	5.267	-5.368	1.00	41.06	B	C
ATOM	1981	C	GLY	B	25	35.613	3.879	-4.757	1.00	40.74	B	C
ATOM	1982	O	GLY	B	25	34.735	3.069	-5.061	1.00	41.00	B	O
ATOM	1983	N	LEU	B	26	36.579	3.599	-3.888	1.00	39.39	B	N
ATOM	1984	CA	LEU	B	26	36.656	2.302	-3.237	1.00	38.36	B	C
ATOM	1985	CB	LEU	B	26	37.760	2.316	-2.182	1.00	36.59	B	C
ATOM	1986	CG	LEU	B	26	39.174	2.447	-2.745	1.00	34.96	B	C
ATOM	1987	CD1	LEU	B	26	40.120	2.868	-1.644	1.00	35.92	B	C
ATOM	1988	CD2	LEU	B	26	39.604	1.135	-3.365	1.00	32.64	B	C
ATOM	1989	C	LEU	B	26	35.338	1.945	-2.578	1.00	39.11	B	C
ATOM	1990	O	LEU	B	26	34.891	0.804	-2.642	1.00	38.61	B	O
ATOM	1991	N	ARG	B	27	34.715	2.932	-1.944	1.00	40.50	B	N
ATOM	1992	CA	ARG	B	27	33.456	2.710	-1.245	1.00	42.03	B	C
ATOM	1993	CB	ARG	B	27	33.084	3.943	-0.427	1.00	42.52	B	C
ATOM	1994	CG	ARG	B	27	33.985	4.189	0.768	1.00	41.95	B	C
ATOM	1995	CD	ARG	B	27	33.460	5.370	1.543	1.00	43.49	B	C
ATOM	1996	NE	ARG	B	27	32.043	5.187	1.840	1.00	42.35	B	N
ATOM	1997	CZ	ARG	B	27	31.577	4.473	2.854	1.00	42.73	B	C
ATOM	1998	NH1	ARG	B	27	32.415	3.869	3.692	1.00	43.63	B	N
ATOM	1999	NH2	ARG	B	27	30.265	4.357	3.025	1.00	43.90	B	N
ATOM	2000	C	ARG	B	27	32.309	2.356	-2.169	1.00	43.02	B	C
ATOM	2001	O	ARG	B	27	31.407	1.621	-1.780	1.00	43.65	B	O
ATOM	2002	N	GLN	B	28	32.336	2.878	-3.389	1.00	44.21	B	N
ATOM	2003	CA	GLN	B	28	31.281	2.583	-4.344	1.00	46.08	B	C
ATOM	2004	CB	GLN	B	28	31.312	3.599	-5.496	1.00	46.77	B	C
ATOM	2005	CG	GLN	B	28	30.352	4.796	-5.298	1.00	49.00	B	C
ATOM	2006	CD	GLN	B	28	28.908	4.502	-5.762	1.00	50.46	B	C
ATOM	2007	OE1	GLN	B	28	27.951	5.151	-5.317	1.00	49.49	B	O
ATOM	2008	NE2	GLN	B	28	28.757	3.536	-6.672	1.00	49.94	B	N
ATOM	2009	C	GLN	B	28	31.399	1.153	-4.889	1.00	47.00	B	C
ATOM	2010	O	GLN	B	28	30.391	0.454	-5.032	1.00	47.29	B	O
ATOM	2011	N	LEU	B	29	32.626	0.718	-5.172	1.00	46.17	B	N
ATOM	2012	CA	LEU	B	29	32.875	-0.622	-5.718	1.00	45.38	B	C
ATOM	2013	CB	LEU	B	29	34.346	-1.018	-5.521	1.00	45.09	B	C
ATOM	2014	CG	LEU	B	29	35.444	-0.186	-6.171	1.00	45.32	B	C
ATOM	2015	CD1	LEU	B	29	36.799	-0.782	-5.796	1.00	45.30	B	C
ATOM	2016	CD2	LEU	B	29	35.280	-0.176	-7.681	1.00	46.01	B	C
ATOM	2017	C	LEU	B	29	32.023	-1.742	-5.137	1.00	44.63	B	C
ATOM	2018	O	LEU	B	29	31.690	-1.740	-3.952	1.00	43.46	B	O
ATOM	2019	N	ALA	B	30	31.675	-2.708	-5.984	1.00	44.88	B	N
ATOM	2020	CA	ALA	B	30	30.909	-3.873	-5.541	1.00	45.37	B	C
ATOM	2021	CB	ALA	B	30	29.766	-4.174	-6.518	1.00	45.11	B	C
ATOM	2022	C	ALA	B	30	31.938	-5.004	-5.552	1.00	45.01	B	C
ATOM	2023	O	ALA	B	30	32.496	-5.314	-6.603	1.00	45.84	B	O
ATOM	2024	N	LEU	B	31	32.196	-5.606	-4.393	1.00	44.06	B	N
ATOM	2025	CA	LEU	B	31	33.193	-6.665	-4.292	1.00	44.32	B	C
ATOM	2026	CB	LEU	B	31	34.095	-6.376	-3.087	1.00	44.80	B	C
ATOM	2027	CG	LEU	B	31	34.488	-4.892	-2.933	1.00	45.35	B	C
ATOM	2028	CD1	LEU	B	31	35.087	-4.654	-1.545	1.00	44.66	B	C
ATOM	2029	CD2	LEU	B	31	35.466	-4.483	-4.026	1.00	43.74	B	C
ATOM	2030	C	LEU	B	31	32.588	-8.065	-4.172	1.00	44.81	B	C
ATOM	2031	O	LEU	B	31	31.431	-8.223	-3.772	1.00	45.38	B	O
ATOM	2032	N	PRO	B	32	33.369	-9.104	-4.515	1.00	44.52	B	N
ATOM	2033	CD	PRO	B	32	34.652	-9.011	-5.229	1.00	44.20	B	C
ATOM	2034	CA	PRO	B	32	32.921	-10.503	-4.452	1.00	44.93	B	C
ATOM	2035	CB	PRO	B	32	34.034	-11.250	-5.195	1.00	45.12	B	C
ATOM	2036	CG	PRO	B	32	34.581	-10.211	-6.128	1.00	42.82	B	C
ATOM	2037	C	PRO	B	32	32.739	-11.021	-3.020	1.00	45.69	B	C
ATOM	2038	O	PRO	B	32	33.475	-10.638	-2.113	1.00	45.77	B	O
ATOM	2039	N	SER	B	33	31.765	-11.902	-2.816	1.00	45.92	B	N
ATOM	2040	CA	SER	B	33	31.512	-12.437	-1.480	1.00	46.21	B	C
ATOM	2041	CB	SER	B	33	30.258	-13.321	-1.481	1.00	47.75	B	C
ATOM	2042	OG	SER	B	33	30.111	-13.961	-0.216	1.00	48.32	B	O
ATOM	2043	C	SER	B	33	32.659	-13.253	-0.890	1.00	45.04	B	C

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ATOM	2044	O	SER	B	33	32.939	-13.166	0.319	1.00	44.91	B	O
ATOM	2045	N	GLY	B	34	33.314	-14.053	-1.726	1.00	43.46	B	N
ATOM	2046	CA	GLY	B	34	34.398	-14.884	-1.219	1.00	43.32	B	C
ATOM	2047	C	GLY	B	34	35.809	-14.348	-1.370	1.00	41.91	B	C
ATOM	2048	O	GLY	B	34	36.766	-15.129	-1.424	1.00	42.84	B	O
ATOM	2049	N	VAL	B	35	35.956	-13.027	-1.408	1.00	40.61	B	N
ATOM	2050	CA	VAL	B	35	37.268	-12.415	-1.583	1.00	38.68	B	C
ATOM	2051	CB	VAL	B	35	37.380	-11.799	-2.999	1.00	39.03	B	C
ATOM	2052	CG1	VAL	B	35	38.724	-11.128	-3.193	1.00	38.80	B	C
ATOM	2053	CG2	VAL	B	35	37.191	-12.880	-4.037	1.00	40.23	B	C
ATOM	2054	C	VAL	B	35	37.627	-11.340	-0.560	1.00	37.38	B	C
ATOM	2055	O	VAL	B	35	36.962	-10.311	-0.469	1.00	37.36	B	O
ATOM	2056	N	ASP	B	36	38.679	-11.590	0.211	1.00	35.95	B	N
ATOM	2057	CA	ASP	B	36	39.163	-10.626	1.192	1.00	35.03	B	C
ATOM	2058	CB	ASP	B	36	40.201	-11.275	2.112	1.00	36.19	B	C
ATOM	2059	CG	ASP	B	36	39.594	-12.253	3.101	1.00	37.41	B	C
ATOM	2060	OD1	ASP	B	36	40.337	-13.138	3.577	1.00	38.15	B	O
ATOM	2061	OD2	ASP	B	36	38.391	-12.139	3.422	1.00	38.33	B	O
ATOM	2062	C	ASP	B	36	39.846	-9.508	0.394	1.00	34.14	B	C
ATOM	2063	O	ASP	B	36	40.671	-9.776	-0.478	1.00	33.18	B	O
ATOM	2064	N	VAL	B	37	39.499	-8.260	0.686	1.00	33.20	B	N
ATOM	2065	CA	VAL	B	37	40.087	-7.119	-0.009	1.00	31.64	B	C
ATOM	2066	CB	VAL	B	37	39.013	-6.368	-0.837	1.00	31.97	B	C
ATOM	2067	CG1	VAL	B	37	39.600	-5.124	-1.474	1.00	31.19	B	C
ATOM	2068	CG2	VAL	B	37	38.457	-7.289	-1.913	1.00	31.37	B	C
ATOM	2069	C	VAL	B	37	40.724	-6.178	1.018	1.00	32.37	B	C
ATOM	2070	O	VAL	B	37	40.113	-5.838	2.033	1.00	31.75	B	O
ATOM	2071	N	ALA	B	38	41.961	-5.766	0.750	1.00	31.13	B	N
ATOM	2072	CA	ALA	B	38	42.687	-4.884	1.657	1.00	29.80	B	C
ATOM	2073	CB	ALA	B	38	43.627	-5.717	2.523	1.00	30.23	B	C
ATOM	2074	C	ALA	B	38	43.487	-3.805	0.922	1.00	28.30	B	C
ATOM	2075	O	ALA	B	38	43.798	-3.949	-0.258	1.00	27.46	B	O
ATOM	2076	N	VAL	B	39	43.812	-2.722	1.623	1.00	27.33	B	N
ATOM	2077	CA	VAL	B	39	44.615	-1.648	1.036	1.00	27.10	B	C
ATOM	2078	CB	VAL	B	39	43.766	-0.402	0.692	1.00	26.85	B	C
ATOM	2079	CG1	VAL	B	39	42.813	-0.730	-0.429	1.00	26.50	B	C
ATOM	2080	CG2	VAL	B	39	43.002	0.073	1.924	1.00	26.89	B	C
ATOM	2081	C	VAL	B	39	45.722	-1.254	2.012	1.00	26.24	B	C
ATOM	2082	O	VAL	B	39	45.533	-1.290	3.227	1.00	26.15	B	O
ATOM	2083	N	MET	B	40	46.880	-0.895	1.470	1.00	25.21	B	N
ATOM	2084	CA	MET	B	40	48.034	-0.504	2.280	1.00	24.34	B	C
ATOM	2085	CB	MET	B	40	49.247	-1.369	1.923	1.00	23.60	B	C
ATOM	2086	CG	MET	B	40	49.313	-2.739	2.562	1.00	26.47	B	C
ATOM	2087	SD	MET	B	40	48.033	-3.883	2.079	1.00	25.47	B	S
ATOM	2088	CE	MET	B	40	47.533	-4.394	3.603	1.00	22.65	B	C
ATOM	2089	C	MET	B	40	48.396	0.968	2.042	1.00	23.74	B	C
ATOM	2090	O	MET	B	40	49.330	1.276	1.294	1.00	22.64	B	O
ATOM	2091	N	PRO	B	41	47.663	1.900	2.672	1.00	23.57	B	N
ATOM	2092	CD	PRO	B	41	46.465	1.746	3.518	1.00	22.37	B	C
ATOM	2093	CA	PRO	B	41	47.986	3.316	2.466	1.00	22.75	B	C
ATOM	2094	CB	PRO	B	41	46.753	4.030	3.002	1.00	23.05	B	C
ATOM	2095	CG	PRO	B	41	46.291	3.135	4.083	1.00	23.95	B	C
ATOM	2096	C	PRO	B	41	49.248	3.727	3.207	1.00	22.63	B	C
ATOM	2097	O	PRO	B	41	49.689	3.040	4.127	1.00	19.56	B	O
ATOM	2098	N	PRO	B	42	49.860	4.848	2.798	1.00	23.12	B	N
ATOM	2099	CD	PRO	B	42	49.516	5.719	1.666	1.00	22.76	B	C
ATOM	2100	CA	PRO	B	42	51.077	5.320	3.464	1.00	23.38	B	C
ATOM	2101	CB	PRO	B	42	51.463	6.559	2.661	1.00	23.45	B	C
ATOM	2102	CG	PRO	B	42	50.853	6.310	1.322	1.00	23.94	B	C
ATOM	2103	C	PRO	B	42	50.665	5.682	4.878	1.00	22.81	B	C
ATOM	2104	O	PRO	B	42	49.555	6.154	5.100	1.00	23.49	B	O
ATOM	2105	N	CYS	B	43	51.556	5.450	5.824	1.00	23.09	B	N
ATOM	2106	CA	CYS	B	43	51.295	5.737	7.222	1.00	25.85	B	C
ATOM	2107	CB	CYS	B	43	52.627	5.745	7.974	1.00	29.28	B	C
ATOM	2108	SG	CYS	B	43	52.471	5.579	9.763	1.00	38.46	B	S
ATOM	2109	C	CYS	B	43	50.530	7.061	7.451	1.00	25.80	B	C

FIGURE 9 - 32

ATOM	2110	O	CYS	B	43	49.560	7.098	8.207	1.00	25.78	B	O
ATOM	2111	N	LEU	B	44	50.968	8.129	6.789	1.00	25.46	B	N
ATOM	2112	CA	LEU	B	44	50.348	9.453	6.903	1.00	25.93	B	C
ATOM	2113	CB	LEU	B	44	50.945	10.427	5.882	1.00	26.44	B	C
ATOM	2114	CG	LEU	B	44	51.937	11.515	6.276	1.00	27.42	B	C
ATOM	2115	CD1	LEU	B	44	52.042	12.490	5.105	1.00	26.57	B	C
ATOM	2116	CD2	LEU	B	44	51.475	12.250	7.527	1.00	26.20	B	C
ATOM	2117	C	LEU	B	44	48.846	9.465	6.682	1.00	25.07	B	C
ATOM	2118	O	LEU	B	44	48.160	10.333	7.198	1.00	24.58	B	O
ATOM	2119	N	PHE	B	45	48.337	8.514	5.909	1.00	24.12	B	N
ATOM	2120	CA	PHE	B	45	46.919	8.497	5.608	1.00	23.86	B	C
ATOM	2121	CB	PHE	B	45	46.728	8.626	4.093	1.00	23.72	B	C
ATOM	2122	CG	PHE	B	45	47.506	9.756	3.483	1.00	23.20	B	C
ATOM	2123	CD1	PHE	B	45	48.714	9.514	2.836	1.00	21.67	B	C
ATOM	2124	CD2	PHE	B	45	47.049	11.066	3.585	1.00	21.85	B	C
ATOM	2125	CE1	PHE	B	45	49.454	10.555	2.303	1.00	20.18	B	C
ATOM	2126	CE2	PHE	B	45	47.780	12.112	3.055	1.00	22.29	B	C
ATOM	2127	CZ	PHE	B	45	48.988	11.860	2.411	1.00	22.16	B	C
ATOM	2128	C	PHE	B	45	46.128	7.301	6.121	1.00	23.33	B	C
ATOM	2129	O	PHE	B	45	44.947	7.171	5.809	1.00	23.55	B	O
ATOM	2130	N	ILE	B	46	46.765	6.447	6.915	1.00	22.52	B	N
ATOM	2131	CA	ILE	B	46	46.098	5.265	7.439	1.00	22.50	B	C
ATOM	2132	CB	ILE	B	46	47.058	4.433	8.321	1.00	20.37	B	C
ATOM	2133	CG2	ILE	B	46	46.275	3.517	9.224	1.00	20.98	B	C
ATOM	2134	CG1	ILE	B	46	48.016	3.632	7.427	1.00	22.47	B	C
ATOM	2135	CD1	ILE	B	46	48.986	2.731	8.192	1.00	20.92	B	C
ATOM	2136	C	ILE	B	46	44.799	5.537	8.212	1.00	23.39	B	C
ATOM	2137	O	ILE	B	46	43.771	4.920	7.918	1.00	20.35	B	O
ATOM	2138	N	SER	B	47	44.827	6.446	9.188	1.00	23.45	B	N
ATOM	2139	CA	SER	B	47	43.608	6.714	9.951	1.00	25.50	B	C
ATOM	2140	CB	SER	B	47	43.912	7.552	11.200	1.00	24.79	B	C
ATOM	2141	OG	SER	B	47	44.629	8.717	10.864	1.00	31.00	B	O
ATOM	2142	C	SER	B	47	42.540	7.385	9.080	1.00	25.78	B	C
ATOM	2143	O	SER	B	47	41.346	7.165	9.275	1.00	26.07	B	O
ATOM	2144	N	GLN	B	48	42.972	8.177	8.104	1.00	26.97	B	N
ATOM	2145	CA	GLN	B	48	42.045	8.838	7.196	1.00	27.38	B	C
ATOM	2146	CB	GLN	B	48	42.803	9.717	6.205	1.00	27.45	B	C
ATOM	2147	CG	GLN	B	48	41.904	10.585	5.321	1.00	30.13	B	C
ATOM	2148	CD	GLN	B	48	42.656	11.257	4.188	1.00	28.86	B	C
ATOM	2149	OE1	GLN	B	48	43.831	11.605	4.326	1.00	31.46	B	O
ATOM	2150	NE2	GLN	B	48	41.978	11.456	3.064	1.00	29.55	B	N
ATOM	2151	C	GLN	B	48	41.298	7.751	6.418	1.00	29.31	B	C
ATOM	2152	O	GLN	B	48	40.064	7.772	6.305	1.00	29.03	B	O
ATOM	2153	N	VAL	B	49	42.061	6.801	5.882	1.00	28.34	B	N
ATOM	2154	CA	VAL	B	49	41.489	5.711	5.100	1.00	27.85	B	C
ATOM	2155	CB	VAL	B	49	42.604	4.823	4.486	1.00	27.42	B	C
ATOM	2156	CG1	VAL	B	49	42.043	3.468	4.064	1.00	25.19	B	C
ATOM	2157	CG2	VAL	B	49	43.197	5.529	3.266	1.00	26.55	B	C
ATOM	2158	C	VAL	B	49	40.544	4.864	5.934	1.00	28.64	B	C
ATOM	2159	O	VAL	B	49	39.446	4.537	5.495	1.00	28.16	B	O
ATOM	2160	N	ILE	B	50	40.978	4.510	7.138	1.00	29.96	B	N
ATOM	2161	CA	ILE	B	50	40.156	3.715	8.035	1.00	31.54	B	C
ATOM	2162	CB	ILE	B	50	40.939	3.385	9.313	1.00	31.44	B	C
ATOM	2163	CG2	ILE	B	50	39.995	2.936	10.423	1.00	30.95	B	C
ATOM	2164	CG1	ILE	B	50	41.969	2.302	8.987	1.00	31.14	B	C
ATOM	2165	CD1	ILE	B	50	42.959	2.043	10.083	1.00	33.49	B	C
ATOM	2166	C	ILE	B	50	38.853	4.443	8.370	1.00	33.33	B	C
ATOM	2167	O	ILE	B	50	37.763	3.884	8.209	1.00	33.92	B	O
ATOM	2168	N	GLN	B	51	38.950	5.684	8.839	1.00	34.64	B	N
ATOM	2169	CA	GLN	B	51	37.738	6.433	9.137	1.00	36.40	B	C
ATOM	2170	CB	GLN	B	51	38.045	7.902	9.458	1.00	38.21	B	C
ATOM	2171	CG	GLN	B	51	38.580	8.166	10.862	1.00	43.10	B	C
ATOM	2172	CD	GLN	B	51	38.751	9.663	11.163	1.00	46.44	B	C
ATOM	2173	OE1	GLN	B	51	39.322	10.041	12.201	1.00	48.54	B	O
ATOM	2174	NE2	GLN	B	51	38.253	10.518	10.263	1.00	47.05	B	N
ATOM	2175	C	GLN	B	51	36.888	6.384	7.873	1.00	35.62	B	C

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ATOM	2176	O	GLN	B	51	35.723	6.019	7.915	1.00	36.83	B	O
ATOM	2177	N	GLY	B	52	37.505	6.734	6.747	1.00	35.41	B	N
ATOM	2178	CA	GLY	B	52	36.812	6.770	5.469	1.00	34.30	B	C
ATOM	2179	C	GLY	B	52	36.124	5.506	4.977	1.00	34.21	B	C
ATOM	2180	O	GLY	B	52	35.050	5.583	4.374	1.00	35.08	B	O
ATOM	2181	N	LEU	B	53	36.719	4.345	5.219	1.00	34.15	B	N
ATOM	2182	CA	LEU	B	53	36.125	3.096	4.758	1.00	33.93	B	C
ATOM	2183	CB	LEU	B	53	37.215	2.161	4.219	1.00	32.97	B	C
ATOM	2184	CG	LEU	B	53	37.948	2.620	2.962	1.00	31.86	B	C
ATOM	2185	CD1	LEU	B	53	38.983	1.570	2.571	1.00	31.41	B	C
ATOM	2186	CD2	LEU	B	53	36.953	2.844	1.833	1.00	31.36	B	C
ATOM	2187	C	LEU	B	53	35.298	2.351	5.802	1.00	35.02	B	C
ATOM	2188	O	LEU	B	53	34.961	1.182	5.600	1.00	35.57	B	O
ATOM	2189	N	ALA	B	54	34.971	3.002	6.916	1.00	34.86	B	N
ATOM	2190	CA	ALA	B	54	34.164	2.343	7.940	1.00	35.40	B	C
ATOM	2191	CB	ALA	B	54	33.894	3.304	9.107	1.00	36.74	B	C
ATOM	2192	C	ALA	B	54	32.842	1.892	7.300	1.00	35.40	B	C
ATOM	2193	O	ALA	B	54	32.267	2.602	6.470	1.00	33.69	B	O
ATOM	2194	N	GLY	B	55	32.379	0.702	7.671	1.00	36.38	B	N
ATOM	2195	CA	GLY	B	55	31.145	0.187	7.106	1.00	37.79	B	C
ATOM	2196	C	GLY	B	55	31.353	-0.695	5.881	1.00	39.23	B	C
ATOM	2197	O	GLY	B	55	30.442	-1.419	5.474	1.00	39.28	B	O
ATOM	2198	N	LYS	B	56	32.542	-0.635	5.285	1.00	39.48	B	N
ATOM	2199	CA	LYS	B	56	32.850	-1.444	4.108	1.00	39.66	B	C
ATOM	2200	CB	LYS	B	56	33.561	-0.607	3.044	1.00	40.26	B	C
ATOM	2201	CG	LYS	B	56	32.662	0.358	2.307	1.00	42.60	B	C
ATOM	2202	CD	LYS	B	56	31.589	-0.366	1.479	1.00	44.60	B	C
ATOM	2203	CE	LYS	B	56	32.203	-1.248	0.392	1.00	45.54	B	C
ATOM	2204	NZ	LYS	B	56	33.130	-0.480	-0.510	1.00	45.54	B	N
ATOM	2205	C	LYS	B	56	33.726	-2.634	4.474	1.00	39.17	B	C
ATOM	2206	O	LYS	B	56	34.628	-2.522	5.301	1.00	39.65	B	O
ATOM	2207	N	ALA	B	57	33.464	-3.776	3.852	1.00	38.57	B	N
ATOM	2208	CA	ALA	B	57	34.243	-4.970	4.124	1.00	37.40	B	C
ATOM	2209	CB	ALA	B	57	33.455	-6.207	3.715	1.00	37.30	B	C
ATOM	2210	C	ALA	B	57	35.565	-4.895	3.364	1.00	37.00	B	C
ATOM	2211	O	ALA	B	57	35.833	-5.705	2.475	1.00	38.04	B	O
ATOM	2212	N	ILE	B	58	36.369	-3.890	3.705	1.00	35.62	B	N
ATOM	2213	CA	ILE	B	58	37.688	-3.678	3.105	1.00	34.47	B	C
ATOM	2214	CB	ILE	B	58	37.723	-2.430	2.207	1.00	34.20	B	C
ATOM	2215	CG2	ILE	B	58	39.169	-2.054	1.900	1.00	33.74	B	C
ATOM	2216	CG1	ILE	B	58	36.945	-2.688	0.917	1.00	33.60	B	C
ATOM	2217	CD1	ILE	B	58	36.881	-1.489	-0.006	1.00	32.56	B	C
ATOM	2218	C	ILE	B	58	38.681	-3.458	4.241	1.00	34.23	B	C
ATOM	2219	O	ILE	B	58	38.541	-2.512	5.015	1.00	34.54	B	O
ATOM	2220	N	ASP	B	59	39.673	-4.331	4.355	1.00	33.60	B	N
ATOM	2221	CA	ASP	B	59	40.662	-4.197	5.419	1.00	33.57	B	C
ATOM	2222	CB	ASP	B	59	41.273	-5.560	5.759	1.00	34.73	B	C
ATOM	2223	CG	ASP	B	59	40.329	-6.432	6.553	1.00	38.32	B	C
ATOM	2224	OD1	ASP	B	59	39.685	-5.910	7.491	1.00	39.68	B	O
ATOM	2225	OD2	ASP	B	59	40.234	-7.641	6.254	1.00	40.20	B	O
ATOM	2226	C	ASP	B	59	41.771	-3.217	5.061	1.00	32.24	B	C
ATOM	2227	O	ASP	B	59	42.138	-3.074	3.900	1.00	31.91	B	O
ATOM	2228	N	VAL	B	60	42.300	-2.543	6.075	1.00	30.12	B	N
ATOM	2229	CA	VAL	B	60	43.374	-1.579	5.884	1.00	27.95	B	C
ATOM	2230	CB	VAL	B	60	43.024	-0.228	6.526	1.00	26.58	B	C
ATOM	2231	CG1	VAL	B	60	44.227	0.699	6.464	1.00	26.55	B	C
ATOM	2232	CG2	VAL	B	60	41.831	0.383	5.822	1.00	26.18	B	C
ATOM	2233	C	VAL	B	60	44.635	-2.105	6.554	1.00	26.94	B	C
ATOM	2234	O	VAL	B	60	44.603	-2.497	7.719	1.00	25.63	B	O
ATOM	2235	N	GLY	B	61	45.739	-2.128	5.813	1.00	25.42	B	N
ATOM	2236	CA	GLY	B	61	46.990	-2.596	6.380	1.00	26.08	B	C
ATOM	2237	C	GLY	B	61	48.074	-1.541	6.207	1.00	25.45	B	C
ATOM	2238	O	GLY	B	61	47.820	-0.491	5.634	1.00	25.17	B	O
ATOM	2239	N	ALA	B	62	49.278	-1.816	6.699	1.00	25.32	B	N
ATOM	2240	CA	ALA	B	62	50.392	-0.881	6.581	1.00	24.89	B	C
ATOM	2241	CB	ALA	B	62	50.979	-0.601	7.959	1.00	24.37	B	C

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ATOM	2242	C	ALA	B	62	51.473	-1.429	5.644	1.00	24.55	B	C
ATOM	2243	O	ALA	B	62	51.545	-2.633	5.395	1.00	25.32	B	O
ATOM	2244	N	GLN	B	63	52.316	-0.535	5.136	1.00	25.65	B	N
ATOM	2245	CA	GLN	B	63	53.388	-0.905	4.213	1.00	23.99	B	C
ATOM	2246	CB	GLN	B	63	53.651	0.244	3.238	1.00	23.86	B	C
ATOM	2247	CG	GLN	B	63	52.510	0.551	2.285	1.00	22.80	B	C
ATOM	2248	CD	GLN	B	63	52.741	1.826	1.487	1.00	22.27	B	C
ATOM	2249	OE1	GLN	B	63	53.826	2.050	0.953	1.00	25.18	B	O
ATOM	2250	NE2	GLN	B	63	51.713	2.661	1.395	1.00	23.96	B	N
ATOM	2251	C	GLN	B	63	54.692	-1.251	4.926	1.00	23.58	B	C
ATOM	2252	O	GLN	B	63	55.604	-1.809	4.320	1.00	23.14	B	O
ATOM	2253	N	ASN	B	64	54.771	-0.923	6.211	1.00	23.31	B	N
ATOM	2254	CA	ASN	B	64	55.975	-1.172	7.007	1.00	23.10	B	C
ATOM	2255	CB	ASN	B	64	57.072	-0.170	6.599	1.00	23.49	B	C
ATOM	2256	CG	ASN	B	64	58.389	-0.390	7.341	1.00	23.95	B	C
ATOM	2257	OD1	ASN	B	64	58.870	-1.522	7.468	1.00	22.43	B	O
ATOM	2258	ND2	ASN	B	64	58.986	0.699	7.818	1.00	21.25	B	N
ATOM	2259	C	ASN	B	64	55.653	-1.017	8.491	1.00	22.24	B	C
ATOM	2260	O	ASN	B	64	54.641	-0.419	8.842	1.00	22.35	B	O
ATOM	2261	N	SER	B	65	56.507	-1.580	9.347	1.00	22.21	B	N
ATOM	2262	CA	SER	B	65	56.362	-1.505	10.805	1.00	22.61	B	C
ATOM	2263	CB	SER	B	65	55.306	-2.500	11.307	1.00	23.71	B	C
ATOM	2264	OG	SER	B	65	55.520	-3.804	10.803	1.00	24.97	B	O
ATOM	2265	C	SER	B	65	57.718	-1.771	11.477	1.00	23.40	B	C
ATOM	2266	O	SER	B	65	58.641	-2.280	10.837	1.00	23.31	B	O
ATOM	2267	N	ALA	B	66	57.821	-1.440	12.765	1.00	22.39	B	N
ATOM	2268	CA	ALA	B	66	59.066	-1.565	13.537	1.00	23.04	B	C
ATOM	2269	CB	ALA	B	66	58.957	-0.713	14.796	1.00	20.94	B	C
ATOM	2270	C	ALA	B	66	59.589	-2.950	13.926	1.00	23.25	B	C
ATOM	2271	O	ALA	B	66	58.841	-3.922	13.994	1.00	25.29	B	O
ATOM	2272	N	VAL	B	67	60.891	-3.022	14.192	1.00	22.54	B	N
ATOM	2273	CA	VAL	B	67	61.510	-4.272	14.612	1.00	21.56	B	C
ATOM	2274	CB	VAL	B	67	63.055	-4.200	14.535	1.00	21.37	B	C
ATOM	2275	CG1	VAL	B	67	63.499	-4.181	13.079	1.00	20.67	B	C
ATOM	2276	CG2	VAL	B	67	63.568	-2.960	15.263	1.00	18.94	B	C
ATOM	2277	C	VAL	B	67	61.092	-4.590	16.053	1.00	23.27	B	C
ATOM	2278	O	VAL	B	67	61.314	-5.695	16.543	1.00	23.68	B	O
ATOM	2279	N	GLU	B	68	60.498	-3.613	16.732	1.00	23.20	B	N
ATOM	2280	CA	GLU	B	68	60.039	-3.814	18.099	1.00	24.95	B	C
ATOM	2281	CB	GLU	B	68	60.656	-2.765	19.030	1.00	27.14	B	C
ATOM	2282	CG	GLU	B	68	62.183	-2.721	18.948	1.00	32.62	B	C
ATOM	2283	CD	GLU	B	68	62.825	-1.931	20.080	1.00	36.35	B	C
ATOM	2284	OE1	GLU	B	68	62.275	-0.871	20.466	1.00	35.99	B	O
ATOM	2285	OE2	GLU	B	68	63.888	-2.370	20.583	1.00	39.89	B	O
ATOM	2286	C	GLU	B	68	58.508	-3.757	18.113	1.00	24.08	B	C
ATOM	2287	O	GLU	B	68	57.896	-2.968	17.401	1.00	23.63	B	O
ATOM	2288	N	PRO	B	69	57.874	-4.606	18.930	1.00	23.34	B	N
ATOM	2289	CD	PRO	B	69	58.534	-5.617	19.774	1.00	23.98	B	C
ATOM	2290	CA	PRO	B	69	56.413	-4.692	19.050	1.00	23.51	B	C
ATOM	2291	CB	PRO	B	69	56.210	-6.037	19.733	1.00	24.45	B	C
ATOM	2292	CG	PRO	B	69	57.398	-6.112	20.645	1.00	24.76	B	C
ATOM	2293	C	PRO	B	69	55.622	-3.587	19.742	1.00	22.55	B	C
ATOM	2294	O	PRO	B	69	54.514	-3.256	19.295	1.00	20.65	B	O
ATOM	2295	N	MET	B	70	56.168	-3.028	20.822	1.00	21.13	B	N
ATOM	2296	CA	MET	B	70	55.456	-1.996	21.575	1.00	20.07	B	C
ATOM	2297	CB	MET	B	70	55.440	-2.363	23.062	1.00	19.64	B	C
ATOM	2298	CG	MET	B	70	54.888	-3.755	23.355	1.00	21.95	B	C
ATOM	2299	SD	MET	B	70	53.144	-3.966	22.919	1.00	22.78	B	S
ATOM	2300	CE	MET	B	70	52.468	-4.249	24.527	1.00	23.64	B	C
ATOM	2301	C	MET	B	70	56.021	-0.588	21.412	1.00	20.07	B	C
ATOM	2302	O	MET	B	70	57.109	-0.398	20.874	1.00	16.62	B	O
ATOM	2303	N	GLN	B	71	55.268	0.398	21.888	1.00	19.62	B	N
ATOM	2304	CA	GLN	B	71	55.702	1.785	21.815	1.00	21.78	B	C
ATOM	2305	CB	GLN	B	71	54.638	2.699	22.430	1.00	21.26	B	C
ATOM	2306	CG	GLN	B	71	53.318	2.696	21.675	1.00	21.88	B	C
ATOM	2307	CD	GLN	B	71	52.249	3.497	22.381	1.00	25.66	B	C

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ATOM	2308	OE1	GLN	B	71	52.471	4.654	22.751	1.00	25.01	B	O
ATOM	2309	NE2	GLN	B	71	51.080	2.891	22.576	1.00	24.70	B	N
ATOM	2310	C	GLN	B	71	57.029	1.928	22.560	1.00	21.12	B	C
ATOM	2311	O	GLN	B	71	57.272	1.216	23.532	1.00	20.54	B	O
ATOM	2312	N	GLY	B	72	57.893	2.823	22.090	1.00	22.14	B	N
ATOM	2313	CA	GLY	B	72	59.177	3.011	22.744	1.00	24.64	B	C
ATOM	2314	C	GLY	B	72	60.110	4.042	22.125	1.00	24.68	B	C
ATOM	2315	O	GLY	B	72	59.689	4.909	21.363	1.00	23.09	B	O
ATOM	2316	N	ALA	B	73	61.393	3.927	22.453	1.00	25.63	B	N
ATOM	2317	CA	ALA	B	73	62.407	4.856	21.971	1.00	26.60	B	C
ATOM	2318	CB	ALA	B	73	63.506	4.989	23.022	1.00	25.29	B	C
ATOM	2319	C	ALA	B	73	63.025	4.516	20.604	1.00	26.95	B	C
ATOM	2320	O	ALA	B	73	64.211	4.177	20.514	1.00	28.37	B	O
ATOM	2321	N	LEU	B	74	62.223	4.616	19.548	1.00	24.96	B	N
ATOM	2322	CA	LEU	B	74	62.681	4.353	18.187	1.00	23.24	B	C
ATOM	2323	CB	LEU	B	74	62.188	2.987	17.692	1.00	23.03	B	C
ATOM	2324	CG	LEU	B	74	63.057	1.744	17.924	1.00	24.92	B	C
ATOM	2325	CD1	LEU	B	74	62.419	0.541	17.223	1.00	22.55	B	C
ATOM	2326	CD2	LEU	B	74	64.471	1.996	17.386	1.00	21.17	B	C
ATOM	2327	C	LEU	B	74	62.171	5.441	17.247	1.00	23.15	B	C
ATOM	2328	O	LEU	B	74	61.194	5.248	16.530	1.00	23.97	B	O
ATOM	2329	N	THR	B	75	62.846	6.583	17.266	1.00	22.29	B	N
ATOM	2330	CA	THR	B	75	62.505	7.734	16.437	1.00	20.47	B	C
ATOM	2331	CB	THR	B	75	63.629	8.779	16.500	1.00	19.93	B	C
ATOM	2332	OG1	THR	B	75	63.818	9.183	17.861	1.00	19.20	B	O
ATOM	2333	CG2	THR	B	75	63.291	9.979	15.637	1.00	17.55	B	C
ATOM	2334	C	THR	B	75	62.210	7.454	14.961	1.00	20.89	B	C
ATOM	2335	O	THR	B	75	63.006	6.821	14.254	1.00	17.45	B	O
ATOM	2336	N	GLY	B	76	61.063	7.965	14.510	1.00	20.32	B	N
ATOM	2337	CA	GLY	B	76	60.634	7.810	13.128	1.00	21.03	B	C
ATOM	2338	C	GLY	B	76	60.052	6.459	12.762	1.00	21.09	B	C
ATOM	2339	O	GLY	B	76	59.652	6.243	11.623	1.00	20.83	B	O
ATOM	2340	N	GLU	B	77	59.987	5.562	13.738	1.00	20.47	B	N
ATOM	2341	CA	GLU	B	77	59.489	4.198	13.545	1.00	22.74	B	C
ATOM	2342	CB	GLU	B	77	60.444	3.268	14.290	1.00	24.89	B	C
ATOM	2343	CG	GLU	B	77	60.920	2.026	13.586	1.00	29.85	B	C
ATOM	2344	CD	GLU	B	77	61.391	2.277	12.177	1.00	30.41	B	C
ATOM	2345	OE1	GLU	B	77	62.037	3.317	11.921	1.00	33.21	B	O
ATOM	2346	OE2	GLU	B	77	61.113	1.413	11.321	1.00	33.54	B	O
ATOM	2347	C	GLU	B	77	58.050	4.030	14.077	1.00	21.84	B	C
ATOM	2348	O	GLU	B	77	57.682	4.642	15.073	1.00	21.17	B	O
ATOM	2349	N	THR	B	78	57.241	3.206	13.410	1.00	23.32	B	N
ATOM	2350	CA	THR	B	78	55.857	2.960	13.837	1.00	22.87	B	C
ATOM	2351	CB	THR	B	78	54.860	3.033	12.666	1.00	24.53	B	C
ATOM	2352	OG1	THR	B	78	54.961	4.301	12.016	1.00	28.42	B	O
ATOM	2353	CG2	THR	B	78	53.431	2.853	13.178	1.00	23.72	B	C
ATOM	2354	C	THR	B	78	55.706	1.572	14.447	1.00	22.95	B	C
ATOM	2355	O	THR	B	78	55.965	0.562	13.787	1.00	22.65	B	O
ATOM	2356	N	ALA	B	79	55.256	1.511	15.693	1.00	22.05	B	N
ATOM	2357	CA	ALA	B	79	55.085	0.218	16.355	1.00	22.83	B	C
ATOM	2358	CB	ALA	B	79	55.034	0.402	17.868	1.00	22.32	B	C
ATOM	2359	C	ALA	B	79	53.843	-0.546	15.880	1.00	22.52	B	C
ATOM	2360	O	ALA	B	79	52.759	0.023	15.734	1.00	20.58	B	O
ATOM	2361	N	PRO	B	80	53.993	-1.857	15.630	1.00	22.09	B	N
ATOM	2362	CD	PRO	B	80	55.219	-2.666	15.724	1.00	20.76	B	C
ATOM	2363	CA	PRO	B	80	52.866	-2.677	15.177	1.00	21.33	B	C
ATOM	2364	CB	PRO	B	80	53.489	-4.066	15.015	1.00	21.52	B	C
ATOM	2365	CG	PRO	B	80	54.654	-4.049	15.937	1.00	21.13	B	C
ATOM	2366	C	PRO	B	80	51.667	-2.652	16.135	1.00	21.80	B	C
ATOM	2367	O	PRO	B	80	50.524	-2.824	15.706	1.00	22.64	B	O
ATOM	2368	N	SER	B	81	51.918	-2.431	17.425	1.00	22.29	B	N
ATOM	2369	CA	SER	B	81	50.821	-2.363	18.383	1.00	23.19	B	C
ATOM	2370	CB	SER	B	81	51.334	-2.371	19.826	1.00	25.28	B	C
ATOM	2371	OG	SER	B	81	52.140	-1.239	20.104	1.00	29.67	B	O
ATOM	2372	C	SER	B	81	50.026	-1.093	18.120	1.00	23.50	B	C
ATOM	2373	O	SER	B	81	48.818	-1.064	18.335	1.00	23.58	B	O

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ATOM	2374	N	GLN	B	82	50.703	-0.042	17.656	1.00	22.81	B	N
ATOM	2375	CA	GLN	B	82	50.023	1.213	17.344	1.00	23.53	B	C
ATOM	2376	CB	GLN	B	82	51.029	2.348	17.064	1.00	22.55	B	C
ATOM	2377	CG	GLN	B	82	51.823	2.817	18.283	1.00	21.14	B	C
ATOM	2378	CD	GLN	B	82	52.859	3.888	17.951	1.00	23.88	B	C
ATOM	2379	OE1	GLN	B	82	53.787	3.651	17.179	1.00	24.02	B	O
ATOM	2380	NE2	GLN	B	82	52.703	5.074	18.542	1.00	20.77	B	N
ATOM	2381	C	GLN	B	82	49.156	0.973	16.110	1.00	23.36	B	C
ATOM	2382	O	GLN	B	82	48.023	1.433	16.044	1.00	25.01	B	O
ATOM	2383	N	LEU	B	83	49.690	0.242	15.136	1.00	24.28	B	N
ATOM	2384	CA	LEU	B	83	48.948	-0.060	13.916	1.00	23.92	B	C
ATOM	2385	CB	LEU	B	83	49.815	-0.854	12.938	1.00	24.56	B	C
ATOM	2386	CG	LEU	B	83	50.886	-0.056	12.194	1.00	25.89	B	C
ATOM	2387	CD1	LEU	B	83	51.635	-0.990	11.264	1.00	26.43	B	C
ATOM	2388	CD2	LEU	B	83	50.238	1.095	11.413	1.00	24.09	B	C
ATOM	2389	C	LEU	B	83	47.700	-0.854	14.257	1.00	24.04	B	C
ATOM	2390	O	LEU	B	83	46.626	-0.586	13.740	1.00	25.72	B	O
ATOM	2391	N	ALA	B	84	47.850	-1.836	15.135	1.00	23.98	B	N
ATOM	2392	CA	ALA	B	84	46.723	-2.649	15.561	1.00	25.83	B	C
ATOM	2393	CB	ALA	B	84	47.207	-3.776	16.470	1.00	24.41	B	C
ATOM	2394	C	ALA	B	84	45.703	-1.772	16.297	1.00	26.27	B	C
ATOM	2395	O	ALA	B	84	44.507	-1.993	16.197	1.00	24.37	B	O
ATOM	2396	N	ASP	B	85	46.184	-0.769	17.027	1.00	27.62	B	N
ATOM	2397	CA	ASP	B	85	45.295	0.119	17.766	1.00	30.21	B	C
ATOM	2398	CB	ASP	B	85	46.084	0.948	18.782	1.00	34.28	B	C
ATOM	2399	CG	ASP	B	85	46.619	0.109	19.927	1.00	40.65	B	C
ATOM	2400	OD1	ASP	B	85	45.885	-0.787	20.412	1.00	43.31	B	O
ATOM	2401	OD2	ASP	B	85	47.776	0.349	20.355	1.00	45.33	B	O
ATOM	2402	C	ASP	B	85	44.436	1.058	16.907	1.00	29.53	B	C
ATOM	2403	O	ASP	B	85	43.294	1.348	17.270	1.00	30.28	B	O
ATOM	2404	N	VAL	B	86	44.965	1.545	15.788	1.00	28.68	B	N
ATOM	2405	CA	VAL	B	86	44.177	2.435	14.939	1.00	27.61	B	C
ATOM	2406	CB	VAL	B	86	45.064	3.321	14.048	1.00	27.16	B	C
ATOM	2407	CG1	VAL	B	86	45.901	4.223	14.910	1.00	27.71	B	C
ATOM	2408	CG2	VAL	B	86	45.949	2.462	13.158	1.00	26.84	B	C
ATOM	2409	C	VAL	B	86	43.214	1.658	14.054	1.00	27.48	B	C
ATOM	2410	O	VAL	B	86	42.323	2.241	13.436	1.00	27.99	B	O
ATOM	2411	N	GLY	B	87	43.390	0.342	13.990	1.00	27.25	B	N
ATOM	2412	CA	GLY	B	87	42.499	-0.471	13.172	1.00	27.23	B	C
ATOM	2413	C	GLY	B	87	43.102	-1.308	12.053	1.00	27.11	B	C
ATOM	2414	O	GLY	B	87	42.366	-1.923	11.291	1.00	27.58	B	O
ATOM	2415	N	CYS	B	88	44.425	-1.343	11.944	1.00	26.19	B	N
ATOM	2416	CA	CYS	B	88	45.071	-2.130	10.903	1.00	26.54	B	C
ATOM	2417	CB	CYS	B	88	46.531	-1.711	10.739	1.00	26.82	B	C
ATOM	2418	SG	CYS	B	88	46.793	-0.050	10.084	1.00	30.30	B	S
ATOM	2419	C	CYS	B	88	45.016	-3.613	11.262	1.00	25.95	B	C
ATOM	2420	O	CYS	B	88	45.102	-3.981	12.430	1.00	25.20	B	O
ATOM	2421	N	SER	B	89	44.887	-4.461	10.251	1.00	26.81	B	N
ATOM	2422	CA	SER	B	89	44.824	-5.897	10.483	1.00	26.73	B	C
ATOM	2423	CB	SER	B	89	43.467	-6.447	10.015	1.00	27.18	B	C
ATOM	2424	OG	SER	B	89	43.207	-6.122	8.656	1.00	28.77	B	O
ATOM	2425	C	SER	B	89	45.961	-6.655	9.797	1.00	26.65	B	C
ATOM	2426	O	SER	B	89	46.172	-7.833	10.082	1.00	27.15	B	O
ATOM	2427	N	MET	B	90	46.690	-5.977	8.909	1.00	25.25	B	N
ATOM	2428	CA	MET	B	90	47.805	-6.588	8.178	1.00	25.82	B	C
ATOM	2429	CB	MET	B	90	47.390	-6.979	6.749	1.00	24.69	B	C
ATOM	2430	CG	MET	B	90	46.014	-7.603	6.551	1.00	27.70	B	C
ATOM	2431	SD	MET	B	90	45.855	-8.245	4.842	1.00	24.18	B	S
ATOM	2432	CE	MET	B	90	46.387	-9.884	5.113	1.00	26.45	B	C
ATOM	2433	C	MET	B	90	48.982	-5.612	8.043	1.00	25.79	B	C
ATOM	2434	O	MET	B	90	48.830	-4.415	8.263	1.00	27.02	B	O
ATOM	2435	N	VAL	B	91	50.148	-6.134	7.666	1.00	25.33	B	N
ATOM	2436	CA	VAL	B	91	51.336	-5.309	7.441	1.00	23.42	B	C
ATOM	2437	CB	VAL	B	91	52.099	-4.959	8.769	1.00	22.23	B	C
ATOM	2438	CG1	VAL	B	91	52.591	-6.213	9.460	1.00	21.67	B	C
ATOM	2439	CG2	VAL	B	91	53.255	-4.034	8.465	1.00	18.12	B	C

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ATOM	2440	C	VAL	B	91	52.285	-6.016	6.469	1.00	23.94	B	C
ATOM	2441	O	VAL	B	91	52.504	-7.223	6.559	1.00	22.79	B	O
ATOM	2442	N	LEU	B	92	52.814	-5.248	5.522	1.00	23.79	B	N
ATOM	2443	CA	LEU	B	92	53.737	-5.766	4.527	1.00	23.98	B	C
ATOM	2444	CB	LEU	B	92	53.814	-4.824	3.326	1.00	22.62	B	C
ATOM	2445	CG	LEU	B	92	52.504	-4.582	2.571	1.00	22.76	B	C
ATOM	2446	CD1	LEU	B	92	52.767	-3.632	1.402	1.00	20.26	B	C
ATOM	2447	CD2	LEU	B	92	51.932	-5.913	2.075	1.00	21.47	B	C
ATOM	2448	C	LEU	B	92	55.106	-5.883	5.155	1.00	24.17	B	C
ATOM	2449	O	LEU	B	92	55.581	-4.952	5.810	1.00	25.10	B	O
ATOM	2450	N	VAL	B	93	55.748	-7.023	4.959	1.00	23.36	B	N
ATOM	2451	CA	VAL	B	93	57.065	-7.214	5.527	1.00	23.61	B	C
ATOM	2452	CB	VAL	B	93	57.020	-8.210	6.698	1.00	25.20	B	C
ATOM	2453	CG1	VAL	B	93	58.304	-8.145	7.479	1.00	28.50	B	C
ATOM	2454	CG2	VAL	B	93	55.862	-7.876	7.607	1.00	29.55	B	C
ATOM	2455	C	VAL	B	93	58.034	-7.718	4.469	1.00	23.51	B	C
ATOM	2456	O	VAL	B	93	57.742	-8.667	3.733	1.00	21.93	B	O
ATOM	2457	N	GLY	B	94	59.180	-7.057	4.381	1.00	22.72	B	N
ATOM	2458	CA	GLY	B	94	60.187	-7.466	3.422	1.00	24.28	B	C
ATOM	2459	C	GLY	B	94	59.965	-7.105	1.965	1.00	24.47	B	C
ATOM	2460	O	GLY	B	94	60.544	-7.748	1.092	1.00	24.48	B	O
ATOM	2461	N	HIS	B	95	59.156	-6.088	1.679	1.00	24.28	B	N
ATOM	2462	CA	HIS	B	95	58.932	-5.706	0.283	1.00	25.08	B	C
ATOM	2463	CB	HIS	B	95	58.143	-4.400	0.202	1.00	24.85	B	C
ATOM	2464	CG	HIS	B	95	57.621	-4.102	-1.168	1.00	26.23	B	C
ATOM	2465	CD2	HIS	B	95	56.443	-4.416	-1.759	1.00	26.78	B	C
ATOM	2466	ND1	HIS	B	95	58.368	-3.450	-2.126	1.00	26.35	B	N
ATOM	2467	CE1	HIS	B	95	57.674	-3.375	-3.247	1.00	26.25	B	C
ATOM	2468	NE2	HIS	B	95	56.502	-3.954	-3.052	1.00	26.92	B	N
ATOM	2469	C	HIS	B	95	60.289	-5.553	-0.403	1.00	24.08	B	C
ATOM	2470	O	HIS	B	95	61.244	-5.084	0.209	1.00	23.90	B	O
ATOM	2471	N	SER	B	96	60.384	-5.940	-1.670	1.00	24.49	B	N
ATOM	2472	CA	SER	B	96	61.668	-5.862	-2.370	1.00	25.33	B	C
ATOM	2473	CB	SER	B	96	61.548	-6.386	-3.809	1.00	24.26	B	C
ATOM	2474	OG	SER	B	96	60.792	-5.520	-4.632	1.00	26.66	B	O
ATOM	2475	C	SER	B	96	62.280	-4.467	-2.376	1.00	25.73	B	C
ATOM	2476	O	SER	B	96	63.500	-4.321	-2.388	1.00	24.04	B	O
ATOM	2477	N	GLU	B	97	61.438	-3.438	-2.374	1.00	26.85	B	N
ATOM	2478	CA	GLU	B	97	61.962	-2.080	-2.365	1.00	26.82	B	C
ATOM	2479	CB	GLU	B	97	60.823	-1.075	-2.577	1.00	26.75	B	C
ATOM	2480	CG	GLU	B	97	60.407	-0.941	-4.039	1.00	25.34	B	C
ATOM	2481	CD	GLU	B	97	58.975	-0.458	-4.216	1.00	27.26	B	C
ATOM	2482	OE1	GLU	B	97	58.431	0.170	-3.277	1.00	27.65	B	O
ATOM	2483	OE2	GLU	B	97	58.396	-0.695	-5.300	1.00	24.48	B	O
ATOM	2484	C	GLU	B	97	62.713	-1.811	-1.060	1.00	25.77	B	C
ATOM	2485	O	GLU	B	97	63.750	-1.165	-1.055	1.00	26.01	B	O
ATOM	2486	N	ARG	B	98	62.207	-2.333	0.047	1.00	25.51	B	N
ATOM	2487	CA	ARG	B	98	62.871	-2.122	1.322	1.00	25.91	B	C
ATOM	2488	CB	ARG	B	98	61.929	-2.449	2.475	1.00	23.40	B	C
ATOM	2489	CG	ARG	B	98	60.705	-1.550	2.529	1.00	21.77	B	C
ATOM	2490	CD	ARG	B	98	60.006	-1.658	3.867	1.00	18.48	B	C
ATOM	2491	NE	ARG	B	98	60.784	-1.032	4.928	1.00	18.41	B	N
ATOM	2492	CZ	ARG	B	98	60.939	0.280	5.071	1.00	21.13	B	C
ATOM	2493	NH1	ARG	B	98	60.363	1.123	4.222	1.00	20.27	B	N
ATOM	2494	NH2	ARG	B	98	61.682	0.753	6.064	1.00	22.49	B	N
ATOM	2495	C	ARG	B	98	64.148	-2.951	1.442	1.00	28.56	B	C
ATOM	2496	O	ARG	B	98	65.095	-2.554	2.134	1.00	29.22	B	O
ATOM	2497	N	ARG	B	99	64.183	-4.098	0.769	1.00	27.78	B	N
ATOM	2498	CA	ARG	B	99	65.361	-4.943	0.833	1.00	29.08	B	C
ATOM	2499	CB	ARG	B	99	65.035	-6.379	0.411	1.00	28.63	B	C
ATOM	2500	CG	ARG	B	99	64.015	-7.117	1.271	1.00	26.70	B	C
ATOM	2501	CD	ARG	B	99	64.040	-8.594	0.896	1.00	25.52	B	C
ATOM	2502	NE	ARG	B	99	62.891	-9.341	1.395	1.00	24.37	B	N
ATOM	2503	CZ	ARG	B	99	62.976	-10.372	2.227	1.00	22.76	B	C
ATOM	2504	NH1	ARG	B	99	64.157	-10.780	2.670	1.00	21.78	B	N
ATOM	2505	NH2	ARG	B	99	61.881	-11.017	2.589	1.00	23.44	B	N

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ATOM	2506	C	ARG	B	99	66.484	-4.425	-0.061	1.00	30.40	B	C
ATOM	2507	O	ARG	B	99	67.628	-4.328	0.377	1.00	30.42	B	O
ATOM	2508	N	LEU	B	100	66.144	-4.079	-1.303	1.00	31.24	B	N
ATOM	2509	CA	LEU	B	100	67.130	-3.635	-2.290	1.00	32.17	B	C
ATOM	2510	CB	LEU	B	100	66.655	-4.013	-3.698	1.00	33.44	B	C
ATOM	2511	CG	LEU	B	100	66.217	-5.459	-3.949	1.00	34.34	B	C
ATOM	2512	CD1	LEU	B	100	65.988	-5.628	-5.428	1.00	35.69	B	C
ATOM	2513	CD2	LEU	B	100	67.274	-6.442	-3.476	1.00	35.35	B	C
ATOM	2514	C	LEU	B	100	67.498	-2.162	-2.296	1.00	33.08	B	C
ATOM	2515	O	LEU	B	100	68.642	-1.801	-2.584	1.00	33.91	B	O
ATOM	2516	N	ILE	B	101	66.532	-1.305	-2.006	1.00	33.00	B	N
ATOM	2517	CA	ILE	B	101	66.792	0.119	-2.019	1.00	32.71	B	C
ATOM	2518	CB	ILE	B	101	65.565	0.897	-2.561	1.00	31.87	B	C
ATOM	2519	CG2	ILE	B	101	65.877	2.378	-2.636	1.00	32.37	B	C
ATOM	2520	CG1	ILE	B	101	65.219	0.387	-3.966	1.00	34.11	B	C
ATOM	2521	CD1	ILE	B	101	63.967	0.994	-4.573	1.00	34.50	B	C
ATOM	2522	C	ILE	B	101	67.161	0.641	-0.643	1.00	32.97	B	C
ATOM	2523	O	ILE	B	101	67.992	1.541	-0.525	1.00	33.57	B	O
ATOM	2524	N	LEU	B	102	66.559	0.061	0.393	1.00	32.60	B	N
ATOM	2525	CA	LEU	B	102	66.808	0.498	1.758	1.00	32.93	B	C
ATOM	2526	CB	LEU	B	102	65.480	0.645	2.506	1.00	32.48	B	C
ATOM	2527	CG	LEU	B	102	64.450	1.554	1.820	1.00	33.34	B	C
ATOM	2528	CD1	LEU	B	102	63.193	1.629	2.667	1.00	32.88	B	C
ATOM	2529	CD2	LEU	B	102	65.036	2.949	1.609	1.00	33.61	B	C
ATOM	2530	C	LEU	B	102	67.756	-0.385	2.557	1.00	32.70	B	C
ATOM	2531	O	LEU	B	102	68.178	-0.001	3.644	1.00	32.41	B	O
ATOM	2532	N	GLY	B	103	68.074	-1.568	2.030	1.00	32.88	B	N
ATOM	2533	CA	GLY	B	103	69.002	-2.464	2.707	1.00	32.27	B	C
ATOM	2534	C	GLY	B	103	68.496	-3.377	3.817	1.00	33.21	B	C
ATOM	2535	O	GLY	B	103	69.298	-3.917	4.579	1.00	32.63	B	O
ATOM	2536	N	GLU	B	104	67.188	-3.583	3.922	1.00	32.89	B	N
ATOM	2537	CA	GLU	B	104	66.678	-4.444	4.983	1.00	32.85	B	C
ATOM	2538	CB	GLU	B	104	65.158	-4.341	5.074	1.00	34.28	B	C
ATOM	2539	CG	GLU	B	104	64.671	-2.921	5.225	1.00	35.28	B	C
ATOM	2540	CD	GLU	B	104	63.479	-2.801	6.144	1.00	34.52	B	C
ATOM	2541	OE1	GLU	B	104	62.545	-3.622	6.032	1.00	31.46	B	O
ATOM	2542	OE2	GLU	B	104	63.485	-1.864	6.976	1.00	37.20	B	O
ATOM	2543	C	GLU	B	104	67.097	-5.898	4.780	1.00	32.53	B	C
ATOM	2544	O	GLU	B	104	66.818	-6.501	3.740	1.00	32.73	B	O
ATOM	2545	N	SER	B	105	67.766	-6.455	5.786	1.00	31.46	B	N
ATOM	2546	CA	SER	B	105	68.251	-7.825	5.717	1.00	31.24	B	C
ATOM	2547	CB	SER	B	105	69.534	-7.953	6.543	1.00	31.81	B	C
ATOM	2548	OG	SER	B	105	69.296	-7.616	7.897	1.00	32.78	B	O
ATOM	2549	C	SER	B	105	67.211	-8.826	6.210	1.00	31.41	B	C
ATOM	2550	O	SER	B	105	66.206	-8.446	6.822	1.00	32.05	B	O
ATOM	2551	N	ASP	B	106	67.454	-10.107	5.941	1.00	30.19	B	N
ATOM	2552	CA	ASP	B	106	66.534	-11.159	6.365	1.00	31.36	B	C
ATOM	2553	CB	ASP	B	106	67.069	-12.535	5.961	1.00	33.09	B	C
ATOM	2554	CG	ASP	B	106	67.431	-12.613	4.483	1.00	35.40	B	C
ATOM	2555	OD1	ASP	B	106	66.791	-11.908	3.678	1.00	35.72	B	O
ATOM	2556	OD2	ASP	B	106	68.341	-13.396	4.124	1.00	37.24	B	O
ATOM	2557	C	ASP	B	106	66.355	-11.111	7.878	1.00	30.43	B	C
ATOM	2558	O	ASP	B	106	65.303	-11.464	8.408	1.00	29.51	B	O
ATOM	2559	N	GLU	B	107	67.405	-10.658	8.553	1.00	31.76	B	N
ATOM	2560	CA	GLU	B	107	67.448	-10.530	10.009	1.00	31.30	B	C
ATOM	2561	CB	GLU	B	107	68.826	-9.997	10.409	1.00	34.55	B	C
ATOM	2562	CG	GLU	B	107	69.405	-10.534	11.696	1.00	41.41	B	C
ATOM	2563	CD	GLU	B	107	70.888	-10.177	11.845	1.00	46.02	B	C
ATOM	2564	OE1	GLU	B	107	71.563	-10.756	12.735	1.00	47.44	B	O
ATOM	2565	OE2	GLU	B	107	71.377	-9.316	11.068	1.00	48.01	B	O
ATOM	2566	C	GLU	B	107	66.364	-9.548	10.440	1.00	29.88	B	C
ATOM	2567	O	GLU	B	107	65.525	-9.853	11.284	1.00	29.77	B	O
ATOM	2568	N	VAL	B	108	66.403	-8.362	9.847	1.00	29.22	B	N
ATOM	2569	CA	VAL	B	108	65.444	-7.305	10.140	1.00	27.29	B	C
ATOM	2570	CB	VAL	B	108	65.838	-6.009	9.409	1.00	27.08	B	C
ATOM	2571	CG1	VAL	B	108	64.731	-4.969	9.533	1.00	24.41	B	C

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ATOM	2572	CG2	VAL	B	108	67.152	-5.480	9.992	1.00	27.41	B	C
ATOM	2573	C	VAL	B	108	64.032	-7.707	9.733	1.00	26.82	B	C
ATOM	2574	O	VAL	B	108	63.088	-7.524	10.497	1.00	26.60	B	O
ATOM	2575	N	VAL	B	109	63.886	-8.253	8.530	1.00	26.25	B	N
ATOM	2576	CA	VAL	B	109	62.574	-8.673	8.058	1.00	24.93	B	C
ATOM	2577	CB	VAL	B	109	62.658	-9.355	6.666	1.00	24.14	B	C
ATOM	2578	CG1	VAL	B	109	61.339	-10.051	6.337	1.00	26.04	B	C
ATOM	2579	CG2	VAL	B	109	62.960	-8.318	5.593	1.00	24.79	B	C
ATOM	2580	C	VAL	B	109	61.964	-9.655	9.047	1.00	25.08	B	C
ATOM	2581	O	VAL	B	109	60.793	-9.559	9.394	1.00	24.13	B	O
ATOM	2582	N	SER	B	110	62.769	-10.599	9.508	1.00	24.84	B	N
ATOM	2583	CA	SER	B	110	62.266	-11.589	10.429	1.00	27.07	B	C
ATOM	2584	CB	SER	B	110	63.326	-12.640	10.713	1.00	28.86	B	C
ATOM	2585	OG	SER	B	110	62.726	-13.729	11.378	1.00	32.52	B	O
ATOM	2586	C	SER	B	110	61.803	-10.967	11.733	1.00	27.23	B	C
ATOM	2587	O	SER	B	110	60.721	-11.288	12.223	1.00	26.48	B	O
ATOM	2588	N	ARG	B	111	62.624	-10.087	12.302	1.00	26.92	B	N
ATOM	2589	CA	ARG	B	111	62.243	-9.434	13.543	1.00	27.50	B	C
ATOM	2590	CB	ARG	B	111	63.314	-8.435	13.995	1.00	30.02	B	C
ATOM	2591	CG	ARG	B	111	64.340	-9.041	14.937	1.00	33.73	B	C
ATOM	2592	CD	ARG	B	111	64.751	-8.042	16.024	1.00	37.05	B	C
ATOM	2593	NE	ARG	B	111	65.698	-7.046	15.532	1.00	39.08	B	N
ATOM	2594	CZ	ARG	B	111	65.981	-5.907	16.161	1.00	40.34	B	C
ATOM	2595	NH1	ARG	B	111	65.384	-5.616	17.315	1.00	40.62	B	N
ATOM	2596	NH2	ARG	B	111	66.851	-5.050	15.625	1.00	39.48	B	N
ATOM	2597	C	ARG	B	111	60.911	-8.715	13.376	1.00	25.86	B	C
ATOM	2598	O	ARG	B	111	60.084	-8.734	14.280	1.00	25.33	B	O
ATOM	2599	N	LYS	B	112	60.701	-8.100	12.214	1.00	24.77	B	N
ATOM	2600	CA	LYS	B	112	59.462	-7.372	11.948	1.00	25.39	B	C
ATOM	2601	CB	LYS	B	112	59.587	-6.547	10.654	1.00	25.43	B	C
ATOM	2602	CG	LYS	B	112	60.587	-5.391	10.752	1.00	26.37	B	C
ATOM	2603	CD	LYS	B	112	60.548	-4.479	9.522	1.00	25.10	B	C
ATOM	2604	CE	LYS	B	112	61.430	-3.250	9.731	1.00	26.49	B	C
ATOM	2605	NZ	LYS	B	112	61.392	-2.328	8.564	1.00	25.15	B	N
ATOM	2606	C	LYS	B	112	58.272	-8.315	11.849	1.00	24.14	B	C
ATOM	2607	O	LYS	B	112	57.190	-8.031	12.363	1.00	23.48	B	O
ATOM	2608	N	PHE	B	113	58.473	-9.435	11.173	1.00	23.74	B	N
ATOM	2609	CA	PHE	B	113	57.418	-10.426	11.027	1.00	24.41	B	C
ATOM	2610	CB	PHE	B	113	57.974	-11.643	10.274	1.00	22.63	B	C
ATOM	2611	CG	PHE	B	113	56.960	-12.726	9.989	1.00	22.59	B	C
ATOM	2612	CD1	PHE	B	113	56.378	-13.449	11.019	1.00	20.86	B	C
ATOM	2613	CD2	PHE	B	113	56.665	-13.084	8.671	1.00	23.17	B	C
ATOM	2614	CE1	PHE	B	113	55.526	-14.521	10.744	1.00	22.73	B	C
ATOM	2615	CE2	PHE	B	113	55.814	-14.152	8.389	1.00	21.80	B	C
ATOM	2616	CZ	PHE	B	113	55.247	-14.872	9.427	1.00	19.67	B	C
ATOM	2617	C	PHE	B	113	56.973	-10.803	12.443	1.00	23.46	B	C
ATOM	2618	O	PHE	B	113	55.798	-10.710	12.783	1.00	23.49	B	O
ATOM	2619	N	ALA	B	114	57.931	-11.203	13.272	1.00	24.60	B	N
ATOM	2620	CA	ALA	B	114	57.651	-11.592	14.651	1.00	24.80	B	C
ATOM	2621	CB	ALA	B	114	58.936	-12.005	15.335	1.00	24.80	B	C
ATOM	2622	C	ALA	B	114	56.969	-10.473	15.448	1.00	24.78	B	C
ATOM	2623	O	ALA	B	114	55.952	-10.695	16.101	1.00	25.03	B	O
ATOM	2624	N	ALA	B	115	57.530	-9.273	15.388	1.00	24.89	B	N
ATOM	2625	CA	ALA	B	115	56.962	-8.151	16.114	1.00	26.23	B	C
ATOM	2626	CB	ALA	B	115	57.800	-6.893	15.873	1.00	24.51	B	C
ATOM	2627	C	ALA	B	115	55.505	-7.921	15.692	1.00	26.26	B	C
ATOM	2628	O	ALA	B	115	54.618	-7.764	16.532	1.00	28.67	B	O
ATOM	2629	N	ALA	B	116	55.259	-7.915	14.389	1.00	26.25	B	N
ATOM	2630	CA	ALA	B	116	53.913	-7.707	13.876	1.00	25.42	B	C
ATOM	2631	CB	ALA	B	116	53.937	-7.720	12.345	1.00	25.11	B	C
ATOM	2632	C	ALA	B	116	52.916	-8.749	14.403	1.00	26.50	B	C
ATOM	2633	O	ALA	B	116	51.810	-8.398	14.815	1.00	26.19	B	O
ATOM	2634	N	GLN	B	117	53.310	-10.022	14.399	1.00	26.20	B	N
ATOM	2635	CA	GLN	B	117	52.431	-11.101	14.861	1.00	27.92	B	C
ATOM	2636	CB	GLN	B	117	53.020	-12.474	14.514	1.00	28.38	B	C
ATOM	2637	CG	GLN	B	117	53.068	-12.785	13.035	1.00	29.14	B	C

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ATOM	2638	CD	GLN	B	117	53.069	-14.271	12.777	1.00	30.51	B	C
ATOM	2639	OE1	GLN	B	117	53.894	-15.011	13.320	1.00	30.34	B	O
ATOM	2640	NE2	GLN	B	117	52.138	-14.724	11.948	1.00	31.29	B	N
ATOM	2641	C	GLN	B	117	52.117	-11.076	16.356	1.00	28.27	B	C
ATOM	2642	O	GLN	B	117	51.009	-11.424	16.766	1.00	26.72	B	O
ATOM	2643	N	SER	B	118	53.089	-10.696	17.178	1.00	27.52	B	N
ATOM	2644	CA	SER	B	118	52.832	-10.650	18.609	1.00	29.13	B	C
ATOM	2645	CB	SER	B	118	54.130	-10.409	19.384	1.00	30.66	B	C
ATOM	2646	OG	SER	B	118	54.631	-9.115	19.114	1.00	33.25	B	O
ATOM	2647	C	SER	B	118	51.819	-9.543	18.923	1.00	28.89	B	C
ATOM	2648	O	SER	B	118	51.335	-9.447	20.041	1.00	29.05	B	O
ATOM	2649	N	CYS	B	119	51.507	-8.704	17.936	1.00	29.05	B	N
ATOM	2650	CA	CYS	B	119	50.529	-7.633	18.133	1.00	28.47	B	C
ATOM	2651	CB	CYS	B	119	51.063	-6.298	17.589	1.00	29.79	B	C
ATOM	2652	SG	CYS	B	119	52.378	-5.530	18.608	1.00	31.56	B	S
ATOM	2653	C	CYS	B	119	49.201	-7.983	17.458	1.00	28.08	B	C
ATOM	2654	O	CYS	B	119	48.285	-7.163	17.401	1.00	28.18	B	O
ATOM	2655	N	GLY	B	120	49.103	-9.203	16.943	1.00	27.02	B	N
ATOM	2656	CA	GLY	B	120	47.874	-9.633	16.300	1.00	27.65	B	C
ATOM	2657	C	GLY	B	120	47.719	-9.271	14.832	1.00	28.01	B	C
ATOM	2658	O	GLY	B	120	46.670	-9.533	14.241	1.00	28.97	B	O
ATOM	2659	N	LEU	B	121	48.746	-8.674	14.236	1.00	26.53	B	N
ATOM	2660	CA	LEU	B	121	48.672	-8.298	12.832	1.00	25.13	B	C
ATOM	2661	CB	LEU	B	121	49.608	-7.125	12.535	1.00	23.72	B	C
ATOM	2662	CG	LEU	B	121	49.363	-5.788	13.235	1.00	26.83	B	C
ATOM	2663	CD1	LEU	B	121	50.407	-4.766	12.752	1.00	24.68	B	C
ATOM	2664	CD2	LEU	B	121	47.958	-5.292	12.929	1.00	24.19	B	C
ATOM	2665	C	LEU	B	121	49.070	-9.478	11.963	1.00	24.80	B	C
ATOM	2666	O	LEU	B	121	49.839	-10.343	12.387	1.00	23.22	B	O
ATOM	2667	N	VAL	B	122	48.538	-9.514	10.748	1.00	24.46	B	N
ATOM	2668	CA	VAL	B	122	48.855	-10.580	9.812	1.00	23.86	B	C
ATOM	2669	CB	VAL	B	122	47.596	-11.012	9.019	1.00	23.77	B	C
ATOM	2670	CG1	VAL	B	122	47.978	-11.930	7.862	1.00	23.35	B	C
ATOM	2671	CG2	VAL	B	122	46.643	-11.742	9.954	1.00	26.09	B	C
ATOM	2672	C	VAL	B	122	49.933	-10.052	8.866	1.00	24.11	B	C
ATOM	2673	O	VAL	B	122	49.677	-9.184	8.025	1.00	24.01	B	O
ATOM	2674	N	PRO	B	123	51.162	-10.561	8.996	1.00	22.93	B	N
ATOM	2675	CD	PRO	B	123	51.740	-11.471	10.002	1.00	23.87	B	C
ATOM	2676	CA	PRO	B	123	52.195	-10.056	8.100	1.00	23.39	B	C
ATOM	2677	CB	PRO	B	123	53.475	-10.384	8.853	1.00	23.77	B	C
ATOM	2678	CG	PRO	B	123	53.144	-11.706	9.466	1.00	22.10	B	C
ATOM	2679	C	PRO	B	123	52.157	-10.695	6.724	1.00	24.24	B	C
ATOM	2680	O	PRO	B	123	51.905	-11.894	6.591	1.00	25.37	B	O
ATOM	2681	N	VAL	B	124	52.387	-9.869	5.709	1.00	24.10	B	N
ATOM	2682	CA	VAL	B	124	52.446	-10.311	4.323	1.00	24.06	B	C
ATOM	2683	CB	VAL	B	124	51.757	-9.306	3.359	1.00	22.66	B	C
ATOM	2684	CG1	VAL	B	124	52.010	-9.720	1.920	1.00	23.24	B	C
ATOM	2685	CG2	VAL	B	124	50.266	-9.246	3.631	1.00	22.62	B	C
ATOM	2686	C	VAL	B	124	53.937	-10.361	3.982	1.00	24.56	B	C
ATOM	2687	O	VAL	B	124	54.533	-9.342	3.632	1.00	23.15	B	O
ATOM	2688	N	LEU	B	125	54.534	-11.541	4.110	1.00	25.07	B	N
ATOM	2689	CA	LEU	B	125	55.953	-11.713	3.825	1.00	24.63	B	C
ATOM	2690	CB	LEU	B	125	56.466	-13.006	4.453	1.00	24.91	B	C
ATOM	2691	CG	LEU	B	125	57.920	-13.349	4.125	1.00	24.33	B	C
ATOM	2692	CD1	LEU	B	125	58.848	-12.309	4.751	1.00	25.50	B	C
ATOM	2693	CD2	LEU	B	125	58.237	-14.747	4.659	1.00	25.12	B	C
ATOM	2694	C	LEU	B	125	56.234	-11.738	2.338	1.00	23.94	B	C
ATOM	2695	O	LEU	B	125	55.786	-12.644	1.629	1.00	24.25	B	O
ATOM	2696	N	CYS	B	126	56.979	-10.740	1.874	1.00	23.36	B	N
ATOM	2697	CA	CYS	B	126	57.340	-10.615	0.464	1.00	23.33	B	C
ATOM	2698	CB	CYS	B	126	57.399	-9.135	0.057	1.00	24.70	B	C
ATOM	2699	SG	CYS	B	126	55.837	-8.217	0.213	1.00	28.49	B	S
ATOM	2700	C	CYS	B	126	58.691	-11.269	0.168	1.00	23.06	B	C
ATOM	2701	O	CYS	B	126	59.669	-11.031	0.867	1.00	20.87	B	O
ATOM	2702	N	VAL	B	127	58.735	-12.079	-0.886	1.00	23.14	B	N
ATOM	2703	CA	VAL	B	127	59.954	-12.771	-1.298	1.00	22.72	B	C

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ATOM	2704	CB	VAL	B	127	59.889	-14.278	-0.954	1.00	22.50	B	C
ATOM	2705	CG1	VAL	B	127	59.762	-14.451	0.540	1.00	22.33	B	C
ATOM	2706	CG2	VAL	B	127	58.705	-14.932	-1.652	1.00	19.85	B	C
ATOM	2707	C	VAL	B	127	60.104	-12.611	-2.808	1.00	24.27	B	C
ATOM	2708	O	VAL	B	127	59.113	-12.422	-3.507	1.00	24.99	B	O
ATOM	2709	N	GLY	B	128	61.335	-12.676	-3.308	1.00	25.84	B	N
ATOM	2710	CA	GLY	B	128	61.540	-12.533	-4.740	1.00	28.99	B	C
ATOM	2711	C	GLY	B	128	62.991	-12.400	-5.156	1.00	30.79	B	C
ATOM	2712	O	GLY	B	128	63.832	-11.970	-4.365	1.00	30.59	B	O
ATOM	2713	N	GLU	B	129	63.281	-12.774	-6.401	1.00	33.20	B	N
ATOM	2714	CA	GLU	B	129	64.637	-12.706	-6.938	1.00	34.31	B	C
ATOM	2715	CB	GLU	B	129	65.041	-14.036	-7.576	1.00	36.36	B	C
ATOM	2716	CG	GLU	B	129	64.570	-14.182	-9.017	1.00	38.22	B	C
ATOM	2717	CD	GLU	B	129	63.131	-14.661	-9.139	1.00	40.90	B	C
ATOM	2718	OE1	GLU	B	129	62.270	-14.281	-8.308	1.00	40.51	B	O
ATOM	2719	OE2	GLU	B	129	62.861	-15.415	-10.092	1.00	42.53	B	O
ATOM	2720	C	GLU	B	129	64.748	-11.621	-8.001	1.00	35.90	B	C
ATOM	2721	O	GLU	B	129	63.798	-11.372	-8.755	1.00	35.20	B	O
ATOM	2722	N	THR	B	130	65.921	-10.998	-8.067	1.00	36.18	B	N
ATOM	2723	CA	THR	B	130	66.197	-9.944	-9.035	1.00	38.25	B	C
ATOM	2724	CB	THR	B	130	67.409	-9.105	-8.602	1.00	38.49	B	C
ATOM	2725	OG1	THR	B	130	68.596	-9.897	-8.724	1.00	37.57	B	O
ATOM	2726	CG2	THR	B	130	67.269	-8.682	-7.147	1.00	37.17	B	C
ATOM	2727	C	THR	B	130	66.514	-10.564	-10.394	1.00	40.03	B	C
ATOM	2728	O	THR	B	130	66.758	-11.772	-10.498	1.00	40.35	B	O
ATOM	2729	N	ARG	B	131	66.510	-9.732	-11.431	1.00	41.20	B	N
ATOM	2730	CA	ARG	B	131	66.790	-10.179	-12.792	1.00	43.29	B	C
ATOM	2731	CB	ARG	B	131	66.849	-8.972	-13.740	1.00	46.06	B	C
ATOM	2732	CG	ARG	B	131	67.201	-9.308	-15.193	1.00	49.17	B	C
ATOM	2733	CD	ARG	B	131	67.917	-8.116	-15.860	1.00	52.24	B	C
ATOM	2734	NE	ARG	B	131	68.325	-8.411	-17.231	1.00	54.48	B	N
ATOM	2735	CZ	ARG	B	131	69.169	-7.662	-17.944	1.00	56.08	B	C
ATOM	2736	NH1	ARG	B	131	69.707	-6.564	-17.420	1.00	55.93	B	N
ATOM	2737	NH2	ARG	B	131	69.474	-8.010	-19.191	1.00	56.81	B	N
ATOM	2738	C	ARG	B	131	68.102	-10.942	-12.875	1.00	42.45	B	C
ATOM	2739	O	ARG	B	131	68.240	-11.857	-13.681	1.00	42.37	B	O
ATOM	2740	N	ALA	B	132	69.055	-10.558	-12.033	1.00	42.53	B	N
ATOM	2741	CA	ALA	B	132	70.374	-11.173	-12.008	1.00	43.22	B	C
ATOM	2742	CB	ALA	B	132	71.332	-10.295	-11.215	1.00	43.49	B	C
ATOM	2743	C	ALA	B	132	70.366	-12.570	-11.415	1.00	44.09	B	C
ATOM	2744	O	ALA	B	132	71.071	-13.465	-11.887	1.00	43.58	B	O
ATOM	2745	N	GLU	B	133	69.582	-12.746	-10.359	1.00	44.51	B	N
ATOM	2746	CA	GLU	B	133	69.493	-14.037	-9.693	1.00	44.86	B	C
ATOM	2747	CB	GLU	B	133	68.850	-13.858	-8.304	1.00	44.26	B	C
ATOM	2748	CG	GLU	B	133	69.542	-12.790	-7.445	1.00	44.26	B	C
ATOM	2749	CD	GLU	B	133	68.815	-12.489	-6.133	1.00	44.79	B	C
ATOM	2750	OE1	GLU	B	133	67.604	-12.166	-6.182	1.00	43.17	B	O
ATOM	2751	OE2	GLU	B	133	69.463	-12.561	-5.054	1.00	43.65	B	O
ATOM	2752	C	GLU	B	133	68.705	-15.045	-10.533	1.00	44.82	B	C
ATOM	2753	O	GLU	B	133	68.941	-16.251	-10.449	1.00	44.34	B	O
ATOM	2754	N	ARG	B	134	67.773	-14.558	-11.346	1.00	46.19	B	N
ATOM	2755	CA	ARG	B	134	66.980	-15.458	-12.184	1.00	48.45	B	C
ATOM	2756	CB	ARG	B	134	65.745	-14.751	-12.732	1.00	48.08	B	C
ATOM	2757	CG	ARG	B	134	64.800	-15.683	-13.461	1.00	49.27	B	C
ATOM	2758	CD	ARG	B	134	63.567	-14.950	-13.954	1.00	51.86	B	C
ATOM	2759	NE	ARG	B	134	62.506	-15.885	-14.334	1.00	54.78	B	N
ATOM	2760	CZ	ARG	B	134	61.843	-16.653	-13.469	1.00	56.47	B	C
ATOM	2761	NH1	ARG	B	134	62.130	-16.596	-12.170	1.00	56.59	B	N
ATOM	2762	NH2	ARG	B	134	60.898	-17.490	-13.903	1.00	58.06	B	N
ATOM	2763	C	ARG	B	134	67.845	-15.919	-13.349	1.00	49.72	B	C
ATOM	2764	O	ARG	B	134	67.590	-16.967	-13.964	1.00	50.17	B	O
ATOM	2765	N	GLU	B	135	68.864	-15.116	-13.650	1.00	50.18	B	N
ATOM	2766	CA	GLU	B	135	69.797	-15.421	-14.729	1.00	50.10	B	C
ATOM	2767	CB	GLU	B	135	70.588	-14.172	-15.126	1.00	50.99	B	C
ATOM	2768	CG	GLU	B	135	69.747	-13.098	-15.787	1.00	52.01	B	C
ATOM	2769	CD	GLU	B	135	69.216	-13.522	-17.139	1.00	52.98	B	C

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ATOM	2770	OE1	GLU	B	135	69.008	-14.750	-17.340	1.00	53.03	B	O
ATOM	2771	OE2	GLU	B	135	68.994	-12.625	-17.995	1.00	52.29	B	O
ATOM	2772	C	GLU	B	135	70.764	-16.496	-14.287	1.00	49.45	B	C
ATOM	2773	O	GLU	B	135	71.096	-17.389	-15.063	1.00	49.99	B	O
ATOM	2774	N	ALA	B	136	71.223	-16.409	-13.041	1.00	48.59	B	N
ATOM	2775	CA	ALA	B	136	72.170	-17.388	-12.519	1.00	47.60	B	C
ATOM	2776	CB	ALA	B	136	72.982	-16.779	-11.378	1.00	48.53	B	C
ATOM	2777	C	ALA	B	136	71.448	-18.638	-12.040	1.00	47.54	B	C
ATOM	2778	O	ALA	B	136	72.033	-19.490	-11.369	1.00	47.42	B	O
ATOM	2779	N	GLY	B	137	70.172	-18.740	-12.400	1.00	48.02	B	N
ATOM	2780	CA	GLY	B	137	69.366	-19.886	-12.016	1.00	47.64	B	C
ATOM	2781	C	GLY	B	137	69.156	-20.029	-10.521	1.00	47.61	B	C
ATOM	2782	O	GLY	B	137	69.015	-21.150	-10.025	1.00	47.78	B	O
ATOM	2783	N	LYS	B	138	69.127	-18.912	-9.797	1.00	46.70	B	N
ATOM	2784	CA	LYS	B	138	68.944	-18.957	-8.348	1.00	46.65	B	C
ATOM	2785	CB	LYS	B	138	69.907	-17.977	-7.659	1.00	46.87	B	C
ATOM	2786	CG	LYS	B	138	71.042	-18.660	-6.872	1.00	48.78	B	C
ATOM	2787	CD	LYS	B	138	72.280	-18.916	-7.729	1.00	49.16	B	C
ATOM	2788	CE	LYS	B	138	73.061	-17.634	-8.025	1.00	49.49	B	C
ATOM	2789	NZ	LYS	B	138	73.808	-17.101	-6.841	1.00	47.69	B	N
ATOM	2790	C	LYS	B	138	67.511	-18.683	-7.867	1.00	45.56	B	C
ATOM	2791	O	LYS	B	138	67.253	-18.654	-6.661	1.00	45.13	B	O
ATOM	2792	N	THR	B	139	66.591	-18.486	-8.805	1.00	44.29	B	N
ATOM	2793	CA	THR	B	139	65.188	-18.222	-8.482	1.00	43.92	B	C
ATOM	2794	CB	THR	B	139	64.263	-18.545	-9.678	1.00	43.58	B	C
ATOM	2795	OG1	THR	B	139	64.092	-17.376	-10.479	1.00	42.78	B	O
ATOM	2796	CG2	THR	B	139	62.898	-19.016	-9.195	1.00	43.55	B	C
ATOM	2797	C	THR	B	139	64.666	-19.006	-7.282	1.00	43.14	B	C
ATOM	2798	O	THR	B	139	64.202	-18.421	-6.304	1.00	42.23	B	O
ATOM	2799	N	LEU	B	140	64.739	-20.331	-7.371	1.00	42.83	B	N
ATOM	2800	CA	LEU	B	140	64.248	-21.203	-6.312	1.00	43.20	B	C
ATOM	2801	CB	LEU	B	140	64.098	-22.635	-6.840	1.00	43.05	B	C
ATOM	2802	CG	LEU	B	140	63.054	-22.858	-7.948	1.00	44.80	B	C
ATOM	2803	CD1	LEU	B	140	63.216	-24.262	-8.504	1.00	44.05	B	C
ATOM	2804	CD2	LEU	B	140	61.624	-22.648	-7.404	1.00	42.29	B	C
ATOM	2805	C	LEU	B	140	65.130	-21.202	-5.076	1.00	42.63	B	C
ATOM	2806	O	LEU	B	140	64.679	-21.569	-3.991	1.00	42.72	B	O
ATOM	2807	N	GLU	B	141	66.384	-20.790	-5.240	1.00	41.84	B	N
ATOM	2808	CA	GLU	B	141	67.328	-20.751	-4.129	1.00	41.43	B	C
ATOM	2809	CB	GLU	B	141	68.766	-20.772	-4.665	1.00	43.70	B	C
ATOM	2810	CG	GLU	B	141	69.846	-20.775	-3.591	1.00	46.88	B	C
ATOM	2811	CD	GLU	B	141	71.248	-20.980	-4.172	1.00	50.70	B	C
ATOM	2812	OE1	GLU	B	141	71.445	-21.986	-4.904	1.00	50.88	B	O
ATOM	2813	OE2	GLU	B	141	72.150	-20.144	-3.893	1.00	52.00	B	O
ATOM	2814	C	GLU	B	141	67.111	-19.496	-3.288	1.00	39.58	B	C
ATOM	2815	O	GLU	B	141	67.223	-19.521	-2.059	1.00	39.45	B	O
ATOM	2816	N	VAL	B	142	66.804	-18.394	-3.957	1.00	37.70	B	N
ATOM	2817	CA	VAL	B	142	66.581	-17.138	-3.256	1.00	36.79	B	C
ATOM	2818	CB	VAL	B	142	66.536	-15.974	-4.260	1.00	37.75	B	C
ATOM	2819	CG1	VAL	B	142	66.322	-14.650	-3.528	1.00	37.79	B	C
ATOM	2820	CG2	VAL	B	142	67.849	-15.938	-5.037	1.00	36.29	B	C
ATOM	2821	C	VAL	B	142	65.283	-17.216	-2.457	1.00	35.74	B	C
ATOM	2822	O	VAL	B	142	65.277	-17.019	-1.235	1.00	35.29	B	O
ATOM	2823	N	VAL	B	143	64.185	-17.513	-3.142	1.00	33.65	B	N
ATOM	2824	CA	VAL	B	143	62.895	-17.639	-2.473	1.00	33.11	B	C
ATOM	2825	CB	VAL	B	143	61.816	-18.215	-3.438	1.00	31.68	B	C
ATOM	2826	CG1	VAL	B	143	60.549	-18.563	-2.671	1.00	29.65	B	C
ATOM	2827	CG2	VAL	B	143	61.497	-17.198	-4.525	1.00	30.74	B	C
ATOM	2828	C	VAL	B	143	63.027	-18.557	-1.261	1.00	33.33	B	C
ATOM	2829	O	VAL	B	143	62.555	-18.236	-0.165	1.00	34.17	B	O
ATOM	2830	N	ALA	B	144	63.669	-19.704	-1.462	1.00	32.42	B	N
ATOM	2831	CA	ALA	B	144	63.853	-20.666	-0.387	1.00	32.54	B	C
ATOM	2832	CB	ALA	B	144	64.577	-21.910	-0.915	1.00	33.65	B	C
ATOM	2833	C	ALA	B	144	64.623	-20.061	0.781	1.00	31.33	B	C
ATOM	2834	O	ALA	B	144	64.309	-20.329	1.936	1.00	30.69	B	O
ATOM	2835	N	ARG	B	145	65.637	-19.252	0.485	1.00	31.02	B	N

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ATOM	2836	CA	ARG	B	145	66.421	-18.615	1.545	1.00	31.96	B	C
ATOM	2837	CB	ARG	B	145	67.652	-17.893	0.978	1.00	32.01	B	C
ATOM	2838	CG	ARG	B	145	68.436	-17.157	2.059	1.00	32.50	B	C
ATOM	2839	CD	ARG	B	145	69.333	-16.074	1.489	1.00	34.81	B	C
ATOM	2840	NE	ARG	B	145	68.718	-14.745	1.553	1.00	34.65	B	N
ATOM	2841	CZ	ARG	B	145	68.463	-13.989	0.492	1.00	36.06	B	C
ATOM	2842	NH1	ARG	B	145	68.765	-14.434	-0.720	1.00	36.01	B	N
ATOM	2843	NH2	ARG	B	145	67.925	-12.779	0.644	1.00	38.36	B	N
ATOM	2844	C	ARG	B	145	65.586	-17.582	2.305	1.00	31.36	B	C
ATOM	2845	O	ARG	B	145	65.607	-17.537	3.532	1.00	31.43	B	O
ATOM	2846	N	GLN	B	146	64.869	-16.742	1.567	1.00	31.80	B	N
ATOM	2847	CA	GLN	B	146	64.056	-15.706	2.190	1.00	31.49	B	C
ATOM	2848	CB	GLN	B	146	63.451	-14.789	1.122	1.00	32.32	B	C
ATOM	2849	CG	GLN	B	146	64.490	-14.024	0.291	1.00	33.24	B	C
ATOM	2850	CD	GLN	B	146	63.870	-13.245	-0.857	1.00	33.89	B	C
ATOM	2851	OE1	GLN	B	146	63.141	-13.807	-1.679	1.00	36.66	B	O
ATOM	2852	NE2	GLN	B	146	64.164	-11.947	-0.929	1.00	32.77	B	N
ATOM	2853	C	GLN	B	146	62.957	-16.354	3.009	1.00	32.42	B	C
ATOM	2854	O	GLN	B	146	62.724	-15.984	4.158	1.00	32.36	B	O
ATOM	2855	N	LEU	B	147	62.283	-17.332	2.415	1.00	32.71	B	N
ATOM	2856	CA	LEU	B	147	61.209	-18.021	3.111	1.00	33.14	B	C
ATOM	2857	CB	LEU	B	147	60.482	-18.958	2.148	1.00	33.72	B	C
ATOM	2858	CG	LEU	B	147	58.968	-19.089	2.309	1.00	34.18	B	C
ATOM	2859	CD1	LEU	B	147	58.451	-20.102	1.309	1.00	35.74	B	C
ATOM	2860	CD2	LEU	B	147	58.619	-19.517	3.706	1.00	36.43	B	C
ATOM	2861	C	LEU	B	147	61.802	-18.821	4.267	1.00	33.58	B	C
ATOM	2862	O	LEU	B	147	61.248	-18.850	5.371	1.00	32.44	B	O
ATOM	2863	N	GLY	B	148	62.939	-19.462	4.007	1.00	34.35	B	N
ATOM	2864	CA	GLY	B	148	63.600	-20.264	5.025	1.00	33.95	B	C
ATOM	2865	C	GLY	B	148	64.010	-19.498	6.271	1.00	33.58	B	C
ATOM	2866	O	GLY	B	148	63.808	-19.973	7.385	1.00	33.55	B	O
ATOM	2867	N	SER	B	149	64.587	-18.313	6.091	1.00	33.86	B	N
ATOM	2868	CA	SER	B	149	65.018	-17.505	7.228	1.00	34.39	B	C
ATOM	2869	CB	SER	B	149	65.411	-16.102	6.774	1.00	33.76	B	C
ATOM	2870	OG	SER	B	149	66.382	-16.158	5.748	1.00	37.90	B	O
ATOM	2871	C	SER	B	149	63.887	-17.391	8.233	1.00	33.93	B	C
ATOM	2872	O	SER	B	149	64.063	-17.651	9.413	1.00	35.67	B	O
ATOM	2873	N	VAL	B	150	62.714	-17.003	7.759	1.00	33.51	B	N
ATOM	2874	CA	VAL	B	150	61.581	-16.859	8.652	1.00	33.52	B	C
ATOM	2875	CB	VAL	B	150	60.380	-16.249	7.900	1.00	31.38	B	C
ATOM	2876	CG1	VAL	B	150	59.171	-16.135	8.814	1.00	29.87	B	C
ATOM	2877	CG2	VAL	B	150	60.774	-14.878	7.377	1.00	29.06	B	C
ATOM	2878	C	VAL	B	150	61.227	-18.204	9.288	1.00	33.67	B	C
ATOM	2879	O	VAL	B	150	61.143	-18.299	10.505	1.00	33.91	B	O
ATOM	2880	N	ILE	B	151	61.038	-19.241	8.472	1.00	35.00	B	N
ATOM	2881	CA	ILE	B	151	60.715	-20.570	8.994	1.00	34.83	B	C
ATOM	2882	CB	ILE	B	151	60.713	-21.645	7.874	1.00	34.84	B	C
ATOM	2883	CG2	ILE	B	151	60.610	-23.053	8.489	1.00	32.94	B	C
ATOM	2884	CG1	ILE	B	151	59.540	-21.405	6.923	1.00	34.82	B	C
ATOM	2885	CD1	ILE	B	151	59.536	-22.306	5.717	1.00	33.61	B	C
ATOM	2886	C	ILE	B	151	61.731	-20.993	10.048	1.00	35.84	B	C
ATOM	2887	O	ILE	B	151	61.364	-21.412	11.140	1.00	35.24	B	O
ATOM	2888	N	ASP	B	152	63.013	-20.876	9.718	1.00	37.41	B	N
ATOM	2889	CA	ASP	B	152	64.059	-21.275	10.650	1.00	39.98	B	C
ATOM	2890	CB	ASP	B	152	65.435	-21.250	9.961	1.00	40.02	B	C
ATOM	2891	CG	ASP	B	152	65.618	-22.385	8.936	1.00	41.78	B	C
ATOM	2892	OD1	ASP	B	152	64.893	-23.411	9.009	1.00	41.56	B	O
ATOM	2893	OD2	ASP	B	152	66.511	-22.252	8.063	1.00	42.08	B	O
ATOM	2894	C	ASP	B	152	64.096	-20.402	11.908	1.00	41.19	B	C
ATOM	2895	O	ASP	B	152	64.568	-20.841	12.960	1.00	42.08	B	O
ATOM	2896	N	GLU	B	153	63.592	-19.173	11.809	1.00	41.50	B	N
ATOM	2897	CA	GLU	B	153	63.596	-18.256	12.954	1.00	40.89	B	C
ATOM	2898	CB	GLU	B	153	63.871	-16.828	12.475	1.00	42.30	B	C
ATOM	2899	CG	GLU	B	153	65.294	-16.337	12.724	1.00	45.45	B	C
ATOM	2900	CD	GLU	B	153	65.494	-15.831	14.147	1.00	47.37	B	C
ATOM	2901	OE1	GLU	B	153	65.446	-16.655	15.091	1.00	46.76	B	O

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ATOM	2902	OE2	GLU	B	153	65.685	-14.601	14.322	1.00	46.66	B	O
ATOM	2903	C	GLU	B	153	62.304	-18.285	13.763	1.00	39.67	B	C
ATOM	2904	O	GLU	B	153	62.337	-18.293	14.993	1.00	39.87	B	O
ATOM	2905	N	LEU	B	154	61.166	-18.316	13.079	1.00	38.28	B	N
ATOM	2906	CA	LEU	B	154	59.874	-18.335	13.766	1.00	37.35	B	C
ATOM	2907	CB	LEU	B	154	58.958	-17.287	13.144	1.00	38.56	B	C
ATOM	2908	CG	LEU	B	154	59.520	-15.869	13.129	1.00	38.92	B	C
ATOM	2909	CD1	LEU	B	154	58.747	-15.043	12.138	1.00	38.21	B	C
ATOM	2910	CD2	LEU	B	154	59.446	-15.262	14.525	1.00	40.92	B	C
ATOM	2911	C	LEU	B	154	59.154	-19.684	13.772	1.00	36.33	B	C
ATOM	2912	O	LEU	B	154	58.220	-19.890	14.550	1.00	34.85	B	O
ATOM	2913	N	GLY	B	155	59.579	-20.606	12.914	1.00	37.04	B	N
ATOM	2914	CA	GLY	B	155	58.912	-21.902	12.860	1.00	36.15	B	C
ATOM	2915	C	GLY	B	155	57.728	-21.853	11.906	1.00	36.68	B	C
ATOM	2916	O	GLY	B	155	56.984	-20.865	11.868	1.00	36.28	B	O
ATOM	2917	N	VAL	B	156	57.545	-22.920	11.133	1.00	35.24	B	N
ATOM	2918	CA	VAL	B	156	56.472	-22.986	10.149	1.00	33.52	B	C
ATOM	2919	CB	VAL	B	156	56.421	-24.372	9.508	1.00	34.06	B	C
ATOM	2920	CG1	VAL	B	156	55.544	-24.342	8.254	1.00	29.95	B	C
ATOM	2921	CG2	VAL	B	156	57.829	-24.813	9.199	1.00	33.87	B	C
ATOM	2922	C	VAL	B	156	55.097	-22.672	10.705	1.00	32.71	B	C
ATOM	2923	O	VAL	B	156	54.213	-22.219	9.979	1.00	31.42	B	O
ATOM	2924	N	GLY	B	157	54.912	-22.926	11.992	1.00	33.45	B	N
ATOM	2925	CA	GLY	B	157	53.626	-22.659	12.602	1.00	33.58	B	C
ATOM	2926	C	GLY	B	157	53.209	-21.206	12.448	1.00	33.84	B	C
ATOM	2927	O	GLY	B	157	52.031	-20.915	12.259	1.00	34.59	B	O
ATOM	2928	N	ALA	B	158	54.172	-20.291	12.510	1.00	33.02	B	N
ATOM	2929	CA	ALA	B	158	53.866	-18.863	12.401	1.00	32.72	B	C
ATOM	2930	CB	ALA	B	158	55.148	-18.031	12.551	1.00	31.21	B	C
ATOM	2931	C	ALA	B	158	53.170	-18.504	11.095	1.00	32.30	B	C
ATOM	2932	O	ALA	B	158	52.512	-17.470	11.009	1.00	32.08	B	O
ATOM	2933	N	PHE	B	159	53.319	-19.352	10.079	1.00	31.55	B	N
ATOM	2934	CA	PHE	B	159	52.700	-19.090	8.785	1.00	30.15	B	C
ATOM	2935	CB	PHE	B	159	53.396	-19.912	7.698	1.00	28.09	B	C
ATOM	2936	CG	PHE	B	159	54.661	-19.275	7.183	1.00	28.95	B	C
ATOM	2937	CD1	PHE	B	159	54.608	-18.273	6.214	1.00	29.10	B	C
ATOM	2938	CD2	PHE	B	159	55.901	-19.638	7.695	1.00	28.34	B	C
ATOM	2939	CE1	PHE	B	159	55.770	-17.641	5.764	1.00	28.03	B	C
ATOM	2940	CE2	PHE	B	159	57.071	-19.009	7.251	1.00	30.31	B	C
ATOM	2941	CZ	PHE	B	159	57.004	-18.010	6.286	1.00	28.14	B	C
ATOM	2942	C	PHE	B	159	51.187	-19.310	8.759	1.00	29.15	B	C
ATOM	2943	O	PHE	B	159	50.516	-18.900	7.816	1.00	29.06	B	O
ATOM	2944	N	ALA	B	160	50.645	-19.935	9.797	1.00	28.36	B	N
ATOM	2945	CA	ALA	B	160	49.199	-20.155	9.869	1.00	29.28	B	C
ATOM	2946	CB	ALA	B	160	48.850	-21.089	11.034	1.00	29.18	B	C
ATOM	2947	C	ALA	B	160	48.518	-18.806	10.062	1.00	28.57	B	C
ATOM	2948	O	ALA	B	160	47.329	-18.658	9.807	1.00	29.09	B	O
ATOM	2949	N	ARG	B	161	49.283	-17.833	10.546	1.00	29.03	B	N
ATOM	2950	CA	ARG	B	161	48.774	-16.483	10.760	1.00	30.38	B	C
ATOM	2951	CB	ARG	B	161	48.880	-16.097	12.233	1.00	33.51	B	C
ATOM	2952	CG	ARG	B	161	48.003	-16.920	13.161	1.00	38.47	B	C
ATOM	2953	CD	ARG	B	161	48.273	-16.546	14.617	1.00	42.43	B	C
ATOM	2954	NE	ARG	B	161	47.547	-17.410	15.556	1.00	48.87	B	N
ATOM	2955	CZ	ARG	B	161	47.620	-18.744	15.577	1.00	50.97	B	C
ATOM	2956	NH1	ARG	B	161	48.389	-19.390	14.706	1.00	51.93	B	N
ATOM	2957	NH2	ARG	B	161	46.928	-19.436	16.480	1.00	53.25	B	N
ATOM	2958	C	ARG	B	161	49.537	-15.463	9.908	1.00	29.14	B	C
ATOM	2959	O	ARG	B	161	49.798	-14.337	10.340	1.00	30.76	B	O
ATOM	2960	N	ALA	B	162	49.903	-15.854	8.697	1.00	26.93	B	N
ATOM	2961	CA	ALA	B	162	50.609	-14.940	7.819	1.00	25.10	B	C
ATOM	2962	CB	ALA	B	162	52.103	-15.147	7.940	1.00	23.97	B	C
ATOM	2963	C	ALA	B	162	50.162	-15.157	6.385	1.00	25.40	B	C
ATOM	2964	O	ALA	B	162	49.250	-15.948	6.123	1.00	26.64	B	O
ATOM	2965	N	VAL	B	163	50.807	-14.434	5.472	1.00	24.49	B	N
ATOM	2966	CA	VAL	B	163	50.548	-14.507	4.038	1.00	22.85	B	C
ATOM	2967	CB	VAL	B	163	49.520	-13.426	3.611	1.00	21.91	B	C

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ATOM	2968	CG1	VAL	B	163	49.464	-13.308	2.103	1.00	19.95	B	C
ATOM	2969	CG2	VAL	B	163	48.137	-13.784	4.163	1.00	21.94	B	C
ATOM	2970	C	VAL	B	163	51.889	-14.257	3.334	1.00	23.41	B	C
ATOM	2971	O	VAL	B	163	52.754	-13.564	3.879	1.00	23.24	B	O
ATOM	2972	N	VAL	B	164	52.078	-14.847	2.154	1.00	24.25	B	N
ATOM	2973	CA	VAL	B	164	53.313	-14.640	1.391	1.00	23.50	B	C
ATOM	2974	CB	VAL	B	164	54.103	-15.961	1.184	1.00	24.53	B	C
ATOM	2975	CG1	VAL	B	164	55.356	-15.708	0.339	1.00	23.22	B	C
ATOM	2976	CG2	VAL	B	164	54.495	-16.545	2.518	1.00	21.44	B	C
ATOM	2977	C	VAL	B	164	52.984	-14.043	0.027	1.00	25.86	B	C
ATOM	2978	O	VAL	B	164	51.912	-14.296	-0.528	1.00	27.41	B	O
ATOM	2979	N	ALA	B	165	53.903	-13.236	-0.501	1.00	26.27	B	N
ATOM	2980	CA	ALA	B	165	53.727	-12.605	-1.799	1.00	26.39	B	C
ATOM	2981	CB	ALA	B	165	53.356	-11.125	-1.626	1.00	26.44	B	C
ATOM	2982	C	ALA	B	165	55.011	-12.737	-2.616	1.00	27.67	B	C
ATOM	2983	O	ALA	B	165	56.089	-12.301	-2.194	1.00	26.72	B	O
ATOM	2984	N	TYR	B	166	54.894	-13.360	-3.783	1.00	27.21	B	N
ATOM	2985	CA	TYR	B	166	56.038	-13.540	-4.652	1.00	25.91	B	C
ATOM	2986	CB	TYR	B	166	55.917	-14.847	-5.445	1.00	25.86	B	C
ATOM	2987	CG	TYR	B	166	56.958	-15.001	-6.542	1.00	26.86	B	C
ATOM	2988	CD1	TYR	B	166	58.326	-14.907	-6.260	1.00	27.39	B	C
ATOM	2989	CE1	TYR	B	166	59.283	-14.982	-7.283	1.00	27.38	B	C
ATOM	2990	CD2	TYR	B	166	56.574	-15.188	-7.875	1.00	26.41	B	C
ATOM	2991	CE2	TYR	B	166	57.524	-15.267	-8.900	1.00	27.40	B	C
ATOM	2992	CZ	TYR	B	166	58.872	-15.158	-8.600	1.00	28.42	B	C
ATOM	2993	OH	TYR	B	166	59.799	-15.186	-9.626	1.00	29.66	B	O
ATOM	2994	C	TYR	B	166	56.149	-12.362	-5.606	1.00	26.50	B	C
ATOM	2995	O	TYR	B	166	55.275	-12.136	-6.443	1.00	26.34	B	O
ATOM	2996	N	GLU	B	167	57.221	-11.597	-5.453	1.00	27.03	B	N
ATOM	2997	CA	GLU	B	167	57.472	-10.450	-6.312	1.00	27.72	B	C
ATOM	2998	CB	GLU	B	167	58.069	-9.274	-5.540	1.00	28.49	B	C
ATOM	2999	CG	GLU	B	167	57.234	-8.638	-4.463	1.00	30.49	B	C
ATOM	3000	CD	GLU	B	167	57.965	-7.429	-3.881	1.00	31.03	B	C
ATOM	3001	OE1	GLU	B	167	58.238	-6.472	-4.637	1.00	30.63	B	O
ATOM	3002	OE2	GLU	B	167	58.284	-7.445	-2.677	1.00	30.55	B	O
ATOM	3003	C	GLU	B	167	58.521	-10.858	-7.323	1.00	28.43	B	C
ATOM	3004	O	GLU	B	167	59.666	-11.126	-6.953	1.00	27.47	B	O
ATOM	3005	N	PRO	B	168	58.155	-10.925	-8.607	1.00	29.57	B	N
ATOM	3006	CD	PRO	B	168	56.823	-10.892	-9.233	1.00	29.71	B	C
ATOM	3007	CA	PRO	B	168	59.190	-11.305	-9.568	1.00	31.96	B	C
ATOM	3008	CB	PRO	B	168	58.385	-11.803	-10.761	1.00	31.26	B	C
ATOM	3009	CG	PRO	B	168	57.156	-10.926	-10.712	1.00	30.26	B	C
ATOM	3010	C	PRO	B	168	59.982	-10.038	-9.876	1.00	33.86	B	C
ATOM	3011	O	PRO	B	168	59.731	-9.375	-10.879	1.00	35.18	B	O
ATOM	3012	N	VAL	B	169	60.920	-9.692	-8.995	1.00	35.62	B	N
ATOM	3013	CA	VAL	B	169	61.747	-8.493	-9.167	1.00	37.76	B	C
ATOM	3014	CB	VAL	B	169	62.893	-8.464	-8.108	1.00	37.77	B	C
ATOM	3015	CG1	VAL	B	169	63.881	-7.360	-8.425	1.00	38.52	B	C
ATOM	3016	CG2	VAL	B	169	62.309	-8.252	-6.709	1.00	37.87	B	C
ATOM	3017	C	VAL	B	169	62.340	-8.400	-10.578	1.00	39.18	B	C
ATOM	3018	O	VAL	B	169	62.525	-7.309	-11.118	1.00	39.32	B	O
ATOM	3019	N	TRP	B	170	62.632	-9.549	-11.176	1.00	41.82	B	N
ATOM	3020	CA	TRP	B	170	63.194	-9.588	-12.522	1.00	44.07	B	C
ATOM	3021	CB	TRP	B	170	63.504	-11.029	-12.938	1.00	44.78	B	C
ATOM	3022	CG	TRP	B	170	62.351	-11.987	-12.813	1.00	45.78	B	C
ATOM	3023	CD2	TRP	B	170	61.477	-12.417	-13.862	1.00	47.54	B	C
ATOM	3024	CE2	TRP	B	170	60.564	-13.338	-13.296	1.00	47.68	B	C
ATOM	3025	CE3	TRP	B	170	61.375	-12.115	-15.228	1.00	48.19	B	C
ATOM	3026	CD1	TRP	B	170	61.945	-12.643	-11.684	1.00	46.39	B	C
ATOM	3027	NE1	TRP	B	170	60.873	-13.460	-11.967	1.00	47.25	B	N
ATOM	3028	CZ2	TRP	B	170	59.560	-13.961	-14.049	1.00	49.29	B	C
ATOM	3029	CZ3	TRP	B	170	60.380	-12.734	-15.978	1.00	49.26	B	C
ATOM	3030	CH2	TRP	B	170	59.483	-13.649	-15.384	1.00	49.74	B	C
ATOM	3031	C	TRP	B	170	62.293	-8.964	-13.576	1.00	45.28	B	C
ATOM	3032	O	TRP	B	170	62.763	-8.265	-14.470	1.00	45.73	B	O
ATOM	3033	N	ALA	B	171	60.996	-9.211	-13.489	1.00	47.28	B	N

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ATOM	3034	CA	ALA	B	171	60.098	-8.658	-14.492	1.00	49.80	B	C
ATOM	3035	CB	ALA	B	171	58.903	-9.568	-14.669	1.00	49.37	B	C
ATOM	3036	C	ALA	B	171	59.632	-7.251	-14.148	1.00	51.89	B	C
ATOM	3037	O	ALA	B	171	58.445	-6.937	-14.285	1.00	53.16	B	O
ATOM	3038	N	ILE	B	172	60.555	-6.400	-13.701	1.00	53.42	B	N
ATOM	3039	CA	ILE	B	172	60.198	-5.020	-13.351	1.00	55.12	B	C
ATOM	3040	CB	ILE	B	172	60.597	-4.698	-11.892	1.00	55.25	B	C
ATOM	3041	CG2	ILE	B	172	60.362	-3.216	-11.583	1.00	54.98	B	C
ATOM	3042	CG1	ILE	B	172	59.771	-5.561	-10.932	1.00	55.57	B	C
ATOM	3043	CD1	ILE	B	172	60.145	-5.362	-9.479	1.00	56.54	B	C
ATOM	3044	C	ILE	B	172	60.873	-4.027	-14.295	1.00	56.54	B	C
ATOM	3045	O	ILE	B	172	62.071	-3.751	-14.169	1.00	56.11	B	O
ATOM	3046	N	GLY	B	173	60.095	-3.509	-15.248	1.00	58.11	B	N
ATOM	3047	CA	GLY	B	173	60.606	-2.553	-16.214	1.00	60.26	B	C
ATOM	3048	C	GLY	B	173	61.921	-2.950	-16.867	1.00	62.01	B	C
ATOM	3049	O	GLY	B	173	62.510	-2.163	-17.638	1.00	62.13	B	O
ATOM	3050	N	THR	B	174	62.379	-4.171	-16.585	1.00	62.92	B	N
ATOM	3051	CA	THR	B	174	63.637	-4.663	-17.148	1.00	63.93	B	C
ATOM	3052	CB	THR	B	174	64.183	-5.878	-16.330	1.00	64.54	B	C
ATOM	3053	OG1	THR	B	174	65.603	-6.005	-16.534	1.00	65.21	B	O
ATOM	3054	CG2	THR	B	174	63.493	-7.182	-16.779	1.00	63.95	B	C
ATOM	3055	C	THR	B	174	63.445	-5.085	-18.614	1.00	63.82	B	C
ATOM	3056	O	THR	B	174	64.307	-4.822	-19.465	1.00	63.79	B	O
ATOM	3057	N	GLY	B	175	62.312	-5.723	-18.907	1.00	63.47	B	N
ATOM	3058	CA	GLY	B	175	62.048	-6.178	-20.266	1.00	62.81	B	C
ATOM	3059	C	GLY	B	175	61.498	-7.595	-20.282	1.00	62.61	B	C
ATOM	3060	O	GLY	B	175	60.755	-7.980	-21.199	1.00	62.39	B	O
ATOM	3061	N	LEU	B	176	61.877	-8.393	-19.284	1.00	61.59	B	N
ATOM	3062	CA	LEU	B	176	61.371	-9.764	-19.185	1.00	60.50	B	C
ATOM	3063	CB	LEU	B	176	62.196	-10.563	-18.165	1.00	60.36	B	C
ATOM	3064	CG	LEU	B	176	63.698	-10.771	-18.430	1.00	60.12	B	C
ATOM	3065	CD1	LEU	B	176	64.357	-11.347	-17.176	1.00	59.37	B	C
ATOM	3066	CD2	LEU	B	176	63.905	-11.711	-19.626	1.00	59.19	B	C
ATOM	3067	C	LEU	B	176	59.919	-9.636	-18.696	1.00	59.84	B	C
ATOM	3068	O	LEU	B	176	59.469	-8.519	-18.382	1.00	60.15	B	O
ATOM	3069	N	THR	B	177	59.184	-10.754	-18.643	1.00	58.15	B	N
ATOM	3070	CA	THR	B	177	57.794	-10.738	-18.162	1.00	56.05	B	C
ATOM	3071	CB	THR	B	177	56.823	-10.243	-19.271	1.00	56.89	B	C
ATOM	3072	OG1	THR	B	177	57.025	-8.833	-19.478	1.00	56.95	B	O
ATOM	3073	CG2	THR	B	177	55.362	-10.483	-18.869	1.00	56.54	B	C
ATOM	3074	C	THR	B	177	57.338	-12.103	-17.619	1.00	53.43	B	C
ATOM	3075	O	THR	B	177	57.694	-13.148	-18.167	1.00	53.56	B	O
ATOM	3076	N	ALA	B	178	56.550	-12.084	-16.543	1.00	50.38	B	N
ATOM	3077	CA	ALA	B	178	56.078	-13.318	-15.903	1.00	48.18	B	C
ATOM	3078	CB	ALA	B	178	56.136	-13.168	-14.390	1.00	48.52	B	C
ATOM	3079	C	ALA	B	178	54.690	-13.801	-16.304	1.00	46.31	B	C
ATOM	3080	O	ALA	B	178	53.695	-13.083	-16.145	1.00	46.31	B	O
ATOM	3081	N	SER	B	179	54.642	-15.039	-16.793	1.00	43.20	B	N
ATOM	3082	CA	SER	B	179	53.412	-15.690	-17.227	1.00	41.17	B	C
ATOM	3083	CB	SER	B	179	53.736	-16.740	-18.277	1.00	40.66	B	C
ATOM	3084	OG	SER	B	179	54.528	-17.761	-17.687	1.00	39.16	B	O
ATOM	3085	C	SER	B	179	52.763	-16.399	-16.044	1.00	40.48	B	C
ATOM	3086	O	SER	B	179	53.422	-16.682	-15.039	1.00	39.23	B	O
ATOM	3087	N	PRO	B	180	51.461	-16.708	-16.153	1.00	39.69	B	N
ATOM	3088	CD	PRO	B	180	50.504	-16.315	-17.204	1.00	39.91	B	C
ATOM	3089	CA	PRO	B	180	50.784	-17.393	-15.051	1.00	38.93	B	C
ATOM	3090	CB	PRO	B	180	49.321	-17.469	-15.521	1.00	39.22	B	C
ATOM	3091	CG	PRO	B	180	49.407	-17.321	-17.016	1.00	40.17	B	C
ATOM	3092	C	PRO	B	180	51.396	-18.758	-14.750	1.00	37.09	B	C
ATOM	3093	O	PRO	B	180	51.335	-19.237	-13.623	1.00	36.21	B	O
ATOM	3094	N	ALA	B	181	52.005	-19.367	-15.760	1.00	35.34	B	N
ATOM	3095	CA	ALA	B	181	52.627	-20.669	-15.585	1.00	34.73	B	C
ATOM	3096	CB	ALA	B	181	52.934	-21.287	-16.947	1.00	34.77	B	C
ATOM	3097	C	ALA	B	181	53.907	-20.548	-14.761	1.00	34.88	B	C
ATOM	3098	O	ALA	B	181	54.139	-21.338	-13.834	1.00	35.30	B	O
ATOM	3099	N	GLN	B	182	54.735	-19.560	-15.102	1.00	33.69	B	N

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ATOM	3100	CA	GLN	B	182	55.988	-19.327	-14.395	1.00	31.64	B	C
ATOM	3101	CB	GLN	B	182	56.782	-18.224	-15.090	1.00	34.31	B	C
ATOM	3102	CG	GLN	B	182	57.297	-18.611	-16.460	1.00	36.71	B	C
ATOM	3103	CD	GLN	B	182	58.078	-17.488	-17.109	1.00	40.11	B	C
ATOM	3104	OE1	GLN	B	182	57.509	-16.464	-17.504	1.00	42.23	B	O
ATOM	3105	NE2	GLN	B	182	59.393	-17.664	-17.211	1.00	41.43	B	N
ATOM	3106	C	GLN	B	182	55.731	-18.941	-12.947	1.00	30.34	B	C
ATOM	3107	O	GLN	B	182	56.480	-19.330	-12.052	1.00	29.53	B	O
ATOM	3108	N	ALA	B	183	54.675	-18.168	-12.716	1.00	29.37	B	N
ATOM	3109	CA	ALA	B	183	54.325	-17.760	-11.360	1.00	29.56	B	C
ATOM	3110	CB	ALA	B	183	53.264	-16.651	-11.393	1.00	28.23	B	C
ATOM	3111	C	ALA	B	183	53.792	-18.981	-10.605	1.00	29.40	B	C
ATOM	3112	O	ALA	B	183	54.158	-19.224	-9.457	1.00	29.35	B	O
ATOM	3113	N	GLN	B	184	52.930	-19.752	-11.263	1.00	30.49	B	N
ATOM	3114	CA	GLN	B	184	52.359	-20.948	-10.656	1.00	30.41	B	C
ATOM	3115	CB	GLN	B	184	51.423	-21.635	-11.658	1.00	29.87	B	C
ATOM	3116	CG	GLN	B	184	50.941	-23.037	-11.275	1.00	28.92	B	C
ATOM	3117	CD	GLN	B	184	50.270	-23.109	-9.911	1.00	28.37	B	C
ATOM	3118	OE1	GLN	B	184	49.463	-22.256	-9.549	1.00	28.04	B	O
ATOM	3119	NE2	GLN	B	184	50.597	-24.145	-9.156	1.00	26.97	B	N
ATOM	3120	C	GLN	B	184	53.470	-21.896	-10.193	1.00	30.23	B	C
ATOM	3121	O	GLN	B	184	53.350	-22.543	-9.149	1.00	30.32	B	O
ATOM	3122	N	GLU	B	185	54.564	-21.956	-10.949	1.00	30.83	B	N
ATOM	3123	CA	GLU	B	185	55.675	-22.833	-10.585	1.00	31.41	B	C
ATOM	3124	CB	GLU	B	185	56.746	-22.878	-11.673	1.00	33.38	B	C
ATOM	3125	CG	GLU	B	185	56.313	-23.541	-12.948	1.00	38.73	B	C
ATOM	3126	CD	GLU	B	185	57.501	-23.979	-13.792	1.00	42.29	B	C
ATOM	3127	OE1	GLU	B	185	58.607	-23.403	-13.617	1.00	43.87	B	O
ATOM	3128	OE2	GLU	B	185	57.325	-24.890	-14.635	1.00	42.49	B	O
ATOM	3129	C	GLU	B	185	56.335	-22.408	-9.297	1.00	28.92	B	C
ATOM	3130	O	GLU	B	185	56.619	-23.249	-8.447	1.00	27.81	B	O
ATOM	3131	N	VAL	B	186	56.601	-21.109	-9.173	1.00	28.30	B	N
ATOM	3132	CA	VAL	B	186	57.233	-20.568	-7.976	1.00	28.55	B	C
ATOM	3133	CB	VAL	B	186	57.555	-19.045	-8.114	1.00	29.78	B	C
ATOM	3134	CG1	VAL	B	186	58.008	-18.497	-6.774	1.00	28.81	B	C
ATOM	3135	CG2	VAL	B	186	58.648	-18.813	-9.149	1.00	29.17	B	C
ATOM	3136	C	VAL	B	186	56.306	-20.757	-6.773	1.00	27.55	B	C
ATOM	3137	O	VAL	B	186	56.729	-21.269	-5.735	1.00	27.55	B	O
ATOM	3138	N	HIS	B	187	55.048	-20.341	-6.909	1.00	26.98	B	N
ATOM	3139	CA	HIS	B	187	54.096	-20.485	-5.810	1.00	27.85	B	C
ATOM	3140	CB	HIS	B	187	52.685	-20.032	-6.230	1.00	28.65	B	C
ATOM	3141	CG	HIS	B	187	52.523	-18.546	-6.332	1.00	28.35	B	C
ATOM	3142	CD2	HIS	B	187	53.308	-17.594	-6.896	1.00	29.26	B	C
ATOM	3143	ND1	HIS	B	187	51.418	-17.885	-5.839	1.00	28.76	B	N
ATOM	3144	CE1	HIS	B	187	51.529	-16.591	-6.095	1.00	28.46	B	C
ATOM	3145	NE2	HIS	B	187	52.666	-16.389	-6.735	1.00	28.04	B	N
ATOM	3146	C	HIS	B	187	54.043	-21.934	-5.311	1.00	28.21	B	C
ATOM	3147	O	HIS	B	187	53.917	-22.174	-4.109	1.00	27.87	B	O
ATOM	3148	N	ALA	B	188	54.145	-22.896	-6.230	1.00	28.24	B	N
ATOM	3149	CA	ALA	B	188	54.110	-24.310	-5.843	1.00	28.15	B	C
ATOM	3150	CB	ALA	B	188	53.946	-25.199	-7.074	1.00	29.39	B	C
ATOM	3151	C	ALA	B	188	55.372	-24.701	-5.075	1.00	26.86	B	C
ATOM	3152	O	ALA	B	188	55.301	-25.441	-4.099	1.00	25.84	B	O
ATOM	3153	N	ALA	B	189	56.521	-24.203	-5.524	1.00	25.71	B	N
ATOM	3154	CA	ALA	B	189	57.792	-24.485	-4.865	1.00	24.90	B	C
ATOM	3155	CB	ALA	B	189	58.946	-23.830	-5.637	1.00	25.61	B	C
ATOM	3156	C	ALA	B	189	57.719	-23.912	-3.453	1.00	25.06	B	C
ATOM	3157	O	ALA	B	189	58.159	-24.533	-2.486	1.00	23.09	B	O
ATOM	3158	N	ILE	B	190	57.161	-22.711	-3.343	1.00	26.46	B	N
ATOM	3159	CA	ILE	B	190	57.012	-22.074	-2.047	1.00	26.43	B	C
ATOM	3160	CB	ILE	B	190	56.351	-20.675	-2.182	1.00	26.87	B	C
ATOM	3161	CG2	ILE	B	190	55.826	-20.212	-0.835	1.00	27.22	B	C
ATOM	3162	CG1	ILE	B	190	57.357	-19.673	-2.758	1.00	25.60	B	C
ATOM	3163	CD1	ILE	B	190	56.762	-18.320	-3.063	1.00	25.00	B	C
ATOM	3164	C	ILE	B	190	56.143	-22.957	-1.154	1.00	26.70	B	C
ATOM	3165	O	ILE	B	190	56.548	-23.329	-0.049	1.00	27.43	B	O

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ATOM	3166	N	ARG	B	191	54.956	-23.308	-1.642	1.00	25.64	B	N
ATOM	3167	CA	ARG	B	191	54.041	-24.132	-0.863	1.00	26.17	B	C
ATOM	3168	CB	ARG	B	191	52.713	-24.314	-1.610	1.00	23.77	B	C
ATOM	3169	CG	ARG	B	191	51.527	-24.471	-0.682	1.00	24.78	B	C
ATOM	3170	CD	ARG	B	191	50.222	-24.654	-1.440	1.00	25.41	B	C
ATOM	3171	NE	ARG	B	191	49.731	-23.438	-2.084	1.00	26.31	B	N
ATOM	3172	CZ	ARG	B	191	49.117	-22.434	-1.457	1.00	26.22	B	C
ATOM	3173	NH1	ARG	B	191	48.913	-22.476	-0.148	1.00	22.57	B	N
ATOM	3174	NH2	ARG	B	191	48.669	-21.400	-2.155	1.00	26.06	B	N
ATOM	3175	C	ARG	B	191	54.661	-25.492	-0.524	1.00	26.48	B	C
ATOM	3176	O	ARG	B	191	54.312	-26.102	0.486	1.00	27.10	B	O
ATOM	3177	N	ALA	B	192	55.592	-25.953	-1.357	1.00	26.70	B	N
ATOM	3178	CA	ALA	B	192	56.265	-27.229	-1.127	1.00	27.50	B	C
ATOM	3179	CB	ALA	B	192	57.010	-27.656	-2.374	1.00	25.81	B	C
ATOM	3180	C	ALA	B	192	57.239	-27.102	0.040	1.00	29.38	B	C
ATOM	3181	O	ALA	B	192	57.342	-27.998	0.890	1.00	28.55	B	O
ATOM	3182	N	GLN	B	193	57.948	-25.977	0.078	1.00	30.48	B	N
ATOM	3183	CA	GLN	B	193	58.916	-25.726	1.133	1.00	31.50	B	C
ATOM	3184	CB	GLN	B	193	59.649	-24.405	0.874	1.00	33.28	B	C
ATOM	3185	CG	GLN	B	193	61.021	-24.323	1.549	1.00	35.78	B	C
ATOM	3186	CD	GLN	B	193	61.643	-22.937	1.481	1.00	36.05	B	C
ATOM	3187	OE1	GLN	B	193	61.711	-22.312	0.417	1.00	36.19	B	O
ATOM	3188	NE2	GLN	B	193	62.113	-22.456	2.624	1.00	35.91	B	N
ATOM	3189	C	GLN	B	193	58.180	-25.678	2.472	1.00	31.70	B	C
ATOM	3190	O	GLN	B	193	58.654	-26.218	3.485	1.00	32.62	B	O
ATOM	3191	N	LEU	B	194	57.009	-25.047	2.471	1.00	30.71	B	N
ATOM	3192	CA	LEU	B	194	56.205	-24.942	3.679	1.00	30.17	B	C
ATOM	3193	CB	LEU	B	194	55.020	-23.992	3.451	1.00	30.51	B	C
ATOM	3194	CG	LEU	B	194	55.353	-22.507	3.231	1.00	31.77	B	C
ATOM	3195	CD1	LEU	B	194	54.078	-21.720	3.021	1.00	32.18	B	C
ATOM	3196	CD2	LEU	B	194	56.116	-21.958	4.432	1.00	31.27	B	C
ATOM	3197	C	LEU	B	194	55.700	-26.320	4.108	1.00	29.61	B	C
ATOM	3198	O	LEU	B	194	55.689	-26.647	5.293	1.00	28.17	B	O
ATOM	3199	N	ALA	B	195	55.307	-27.131	3.132	1.00	28.96	B	N
ATOM	3200	CA	ALA	B	195	54.790	-28.467	3.401	1.00	29.13	B	C
ATOM	3201	CB	ALA	B	195	54.118	-29.014	2.147	1.00	27.53	B	C
ATOM	3202	C	ALA	B	195	55.857	-29.451	3.900	1.00	29.18	B	C
ATOM	3203	O	ALA	B	195	55.551	-30.362	4.672	1.00	29.45	B	O
ATOM	3204	N	ALA	B	196	57.099	-29.274	3.451	1.00	29.67	B	N
ATOM	3205	CA	ALA	B	196	58.197	-30.145	3.868	1.00	32.45	B	C
ATOM	3206	CB	ALA	B	196	59.475	-29.787	3.113	1.00	31.10	B	C
ATOM	3207	C	ALA	B	196	58.422	-30.001	5.369	1.00	34.20	B	C
ATOM	3208	O	ALA	B	196	59.272	-30.672	5.955	1.00	34.40	B	O
ATOM	3209	N	GLU	B	197	57.643	-29.113	5.980	1.00	35.33	B	N
ATOM	3210	CA	GLU	B	197	57.722	-28.865	7.406	1.00	36.79	B	C
ATOM	3211	CB	GLU	B	197	58.214	-27.436	7.642	1.00	39.55	B	C
ATOM	3212	CG	GLU	B	197	59.539	-27.343	8.432	1.00	44.20	B	C
ATOM	3213	CD	GLU	B	197	60.699	-28.100	7.791	1.00	46.09	B	C
ATOM	3214	OE1	GLU	B	197	61.722	-28.309	8.481	1.00	47.67	B	O
ATOM	3215	OE2	GLU	B	197	60.600	-28.481	6.603	1.00	48.81	B	O
ATOM	3216	C	GLU	B	197	56.339	-29.096	8.023	1.00	36.65	B	C
ATOM	3217	O	GLU	B	197	56.212	-29.783	9.038	1.00	36.92	B	O
ATOM	3218	N	ASN	B	198	55.301	-28.543	7.399	1.00	35.53	B	N
ATOM	3219	CA	ASN	B	198	53.943	-28.724	7.895	1.00	35.08	B	C
ATOM	3220	CB	ASN	B	198	53.643	-27.717	8.997	1.00	36.56	B	C
ATOM	3221	CG	ASN	B	198	52.380	-28.055	9.751	1.00	37.94	B	C
ATOM	3222	OD1	ASN	B	198	51.289	-28.084	9.171	1.00	38.94	B	O
ATOM	3223	ND2	ASN	B	198	52.514	-28.322	11.049	1.00	36.92	B	N
ATOM	3224	C	ASN	B	198	52.919	-28.594	6.769	1.00	34.22	B	C
ATOM	3225	O	ASN	B	198	52.688	-27.506	6.239	1.00	32.52	B	O
ATOM	3226	N	ALA	B	199	52.297	-29.722	6.424	1.00	34.16	B	N
ATOM	3227	CA	ALA	B	199	51.326	-29.783	5.340	1.00	32.28	B	C
ATOM	3228	CB	ALA	B	199	51.050	-31.229	4.993	1.00	33.24	B	C
ATOM	3229	C	ALA	B	199	50.018	-29.040	5.585	1.00	32.41	B	C
ATOM	3230	O	ALA	B	199	49.507	-28.380	4.675	1.00	31.17	B	O
ATOM	3231	N	GLU	B	200	49.463	-29.152	6.791	1.00	32.39	B	N

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ATOM	3232	CA	GLU	B	200	48.217	-28.449	7.106	1.00	33.82	B	C
ATOM	3233	CB	GLU	B	200	47.748	-28.778	8.542	1.00	37.63	B	C
ATOM	3234	CG	GLU	B	200	46.715	-29.924	8.609	1.00	43.68	B	C
ATOM	3235	CD	GLU	B	200	46.261	-30.289	10.033	1.00	46.22	B	C
ATOM	3236	OE1	GLU	B	200	47.004	-31.015	10.738	1.00	47.59	B	O
ATOM	3237	OE2	GLU	B	200	45.155	-29.859	10.447	1.00	46.45	B	O
ATOM	3238	C	GLU	B	200	48.406	-26.933	6.949	1.00	32.04	B	C
ATOM	3239	O	GLU	B	200	47.594	-26.252	6.327	1.00	30.76	B	O
ATOM	3240	N	VAL	B	201	49.489	-26.408	7.510	1.00	30.66	B	N
ATOM	3241	CA	VAL	B	201	49.764	-24.980	7.422	1.00	29.45	B	C
ATOM	3242	CB	VAL	B	201	51.005	-24.599	8.275	1.00	30.60	B	C
ATOM	3243	CG1	VAL	B	201	51.337	-23.113	8.088	1.00	27.46	B	C
ATOM	3244	CG2	VAL	B	201	50.737	-24.901	9.743	1.00	29.55	B	C
ATOM	3245	C	VAL	B	201	50.000	-24.548	5.971	1.00	28.04	B	C
ATOM	3246	O	VAL	B	201	49.561	-23.477	5.555	1.00	26.32	B	O
ATOM	3247	N	ALA	B	202	50.694	-25.389	5.206	1.00	27.23	B	N
ATOM	3248	CA	ALA	B	202	50.992	-25.085	3.809	1.00	26.26	B	C
ATOM	3249	CB	ALA	B	202	51.969	-26.111	3.249	1.00	25.10	B	C
ATOM	3250	C	ALA	B	202	49.726	-25.041	2.959	1.00	27.08	B	C
ATOM	3251	O	ALA	B	202	49.596	-24.204	2.066	1.00	27.99	B	O
ATOM	3252	N	LYS	B	203	48.787	-25.939	3.239	1.00	27.48	B	N
ATOM	3253	CA	LYS	B	203	47.536	-25.969	2.490	1.00	28.78	B	C
ATOM	3254	CB	LYS	B	203	46.697	-27.186	2.892	1.00	30.07	B	C
ATOM	3255	CG	LYS	B	203	45.575	-27.496	1.916	1.00	33.81	B	C
ATOM	3256	CD	LYS	B	203	44.718	-28.676	2.366	1.00	34.36	B	C
ATOM	3257	CE	LYS	B	203	43.897	-28.334	3.603	1.00	36.47	B	C
ATOM	3258	NZ	LYS	B	203	43.051	-29.489	4.029	1.00	38.73	B	N
ATOM	3259	C	LYS	B	203	46.728	-24.694	2.744	1.00	28.51	B	C
ATOM	3260	O	LYS	B	203	46.039	-24.198	1.854	1.00	27.63	B	O
ATOM	3261	N	GLY	B	204	46.830	-24.154	3.954	1.00	27.86	B	N
ATOM	3262	CA	GLY	B	204	46.070	-22.960	4.289	1.00	27.62	B	C
ATOM	3263	C	GLY	B	204	46.677	-21.584	4.032	1.00	26.42	B	C
ATOM	3264	O	GLY	B	204	45.949	-20.596	4.018	1.00	26.36	B	O
ATOM	3265	N	VAL	B	205	47.984	-21.488	3.816	1.00	26.55	B	N
ATOM	3266	CA	VAL	B	205	48.589	-20.169	3.601	1.00	27.10	B	C
ATOM	3267	CB	VAL	B	205	50.122	-20.207	3.796	1.00	27.93	B	C
ATOM	3268	CG1	VAL	B	205	50.747	-21.118	2.763	1.00	28.76	B	C
ATOM	3269	CG2	VAL	B	205	50.697	-18.800	3.678	1.00	24.35	B	C
ATOM	3270	C	VAL	B	205	48.310	-19.563	2.227	1.00	27.01	B	C
ATOM	3271	O	VAL	B	205	48.490	-20.217	1.209	1.00	27.26	B	O
ATOM	3272	N	ARG	B	206	47.870	-18.308	2.201	1.00	25.82	B	N
ATOM	3273	CA	ARG	B	206	47.600	-17.638	0.927	1.00	26.53	B	C
ATOM	3274	CB	ARG	B	206	46.687	-16.419	1.125	1.00	26.75	B	C
ATOM	3275	CG	ARG	B	206	45.214	-16.753	1.374	1.00	29.27	B	C
ATOM	3276	CD	ARG	B	206	44.908	-17.052	2.835	1.00	30.81	B	C
ATOM	3277	NE	ARG	B	206	44.760	-15.832	3.624	1.00	30.34	B	N
ATOM	3278	CZ	ARG	B	206	43.831	-14.901	3.414	1.00	31.50	B	C
ATOM	3279	NH1	ARG	B	206	42.944	-15.035	2.432	1.00	31.31	B	N
ATOM	3280	NH2	ARG	B	206	43.794	-13.823	4.184	1.00	32.17	B	N
ATOM	3281	C	ARG	B	206	48.905	-17.185	0.275	1.00	24.59	B	C
ATOM	3282	O	ARG	B	206	49.770	-16.618	0.936	1.00	22.91	B	O
ATOM	3283	N	LEU	B	207	49.046	-17.442	-1.022	1.00	24.36	B	N
ATOM	3284	CA	LEU	B	207	50.248	-17.030	-1.746	1.00	25.63	B	C
ATOM	3285	CB	LEU	B	207	50.970	-18.250	-2.326	1.00	23.92	B	C
ATOM	3286	CG	LEU	B	207	51.319	-19.372	-1.342	1.00	25.33	B	C
ATOM	3287	CD1	LEU	B	207	52.076	-20.476	-2.076	1.00	24.00	B	C
ATOM	3288	CD2	LEU	B	207	52.164	-18.824	-0.195	1.00	22.67	B	C
ATOM	3289	C	LEU	B	207	49.828	-16.067	-2.859	1.00	26.13	B	C
ATOM	3290	O	LEU	B	207	49.164	-16.467	-3.822	1.00	26.25	B	O
ATOM	3291	N	LEU	B	208	50.225	-14.802	-2.716	1.00	24.98	B	N
ATOM	3292	CA	LEU	B	208	49.863	-13.753	-3.665	1.00	24.42	B	C
ATOM	3293	CB	LEU	B	208	49.554	-12.464	-2.905	1.00	22.86	B	C
ATOM	3294	CG	LEU	B	208	48.660	-12.575	-1.665	1.00	22.52	B	C
ATOM	3295	CD1	LEU	B	208	48.457	-11.201	-1.071	1.00	18.27	B	C
ATOM	3296	CD2	LEU	B	208	47.323	-13.207	-2.031	1.00	22.76	B	C
ATOM	3297	C	LEU	B	208	50.903	-13.437	-4.741	1.00	25.81	B	C

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ATOM	3298	O	LEU	B	208	52.118	-13.451	-4.484	1.00	25.29	B	O
ATOM	3299	N	TYR	B	209	50.415	-13.160	-5.951	1.00	26.27	B	N
ATOM	3300	CA	TYR	B	209	51.295	-12.791	-7.046	1.00	27.62	B	C
ATOM	3301	CB	TYR	B	209	50.670	-13.059	-8.420	1.00	28.27	B	C
ATOM	3302	CG	TYR	B	209	51.626	-12.712	-9.545	1.00	29.06	B	C
ATOM	3303	CD1	TYR	B	209	52.854	-13.369	-9.654	1.00	27.93	B	C
ATOM	3304	CE1	TYR	B	209	53.783	-13.002	-10.618	1.00	28.72	B	C
ATOM	3305	CD2	TYR	B	209	51.346	-11.677	-10.450	1.00	29.16	B	C
ATOM	3306	CE2	TYR	B	209	52.279	-11.302	-11.436	1.00	28.94	B	C
ATOM	3307	CZ	TYR	B	209	53.496	-11.971	-11.500	1.00	30.32	B	C
ATOM	3308	OH	TYR	B	209	54.465	-11.590	-12.402	1.00	32.26	B	O
ATOM	3309	C	TYR	B	209	51.527	-11.294	-6.889	1.00	29.10	B	C
ATOM	3310	O	TYR	B	209	50.586	-10.487	-6.966	1.00	26.36	B	O
ATOM	3311	N	GLY	B	210	52.784	-10.941	-6.659	1.00	30.08	B	N
ATOM	3312	CA	GLY	B	210	53.146	-9.552	-6.464	1.00	32.80	B	C
ATOM	3313	C	GLY	B	210	53.784	-8.929	-7.677	1.00	33.52	B	C
ATOM	3314	O	GLY	B	210	54.364	-7.855	-7.588	1.00	34.14	B	O
ATOM	3315	N	GLY	B	211	53.688	-9.611	-8.812	1.00	35.13	B	N
ATOM	3316	CA	GLY	B	211	54.247	-9.072	-10.035	1.00	35.98	B	C
ATOM	3317	C	GLY	B	211	53.200	-8.158	-10.631	1.00	37.88	B	C
ATOM	3318	O	GLY	B	211	52.224	-7.813	-9.961	1.00	37.69	B	O
ATOM	3319	N	SER	B	212	53.373	-7.780	-11.889	1.00	38.64	B	N
ATOM	3320	CA	SER	B	212	52.418	-6.890	-12.533	1.00	41.16	B	C
ATOM	3321	CB	SER	B	212	52.854	-6.646	-13.982	1.00	40.83	B	C
ATOM	3322	OG	SER	B	212	52.068	-5.635	-14.591	1.00	41.26	B	O
ATOM	3323	C	SER	B	212	50.984	-7.450	-12.492	1.00	42.18	B	C
ATOM	3324	O	SER	B	212	50.730	-8.574	-12.938	1.00	42.76	B	O
ATOM	3325	N	VAL	B	213	50.046	-6.672	-11.959	1.00	42.66	B	N
ATOM	3326	CA	VAL	B	213	48.653	-7.120	-11.879	1.00	43.45	B	C
ATOM	3327	CB	VAL	B	213	48.237	-7.470	-10.420	1.00	44.23	B	C
ATOM	3328	CG1	VAL	B	213	46.788	-7.940	-10.396	1.00	43.22	B	C
ATOM	3329	CG2	VAL	B	213	49.148	-8.542	-9.842	1.00	44.22	B	C
ATOM	3330	C	VAL	B	213	47.687	-6.053	-12.382	1.00	43.88	B	C
ATOM	3331	O	VAL	B	213	47.430	-5.069	-11.688	1.00	43.96	B	O
ATOM	3332	N	LYS	B	214	47.159	-6.256	-13.587	1.00	44.72	B	N
ATOM	3333	CA	LYS	B	214	46.206	-5.330	-14.201	1.00	45.10	B	C
ATOM	3334	CB	LYS	B	214	46.758	-4.793	-15.528	1.00	45.51	B	C
ATOM	3335	CG	LYS	B	214	48.041	-3.964	-15.383	1.00	47.57	B	C
ATOM	3336	CD	LYS	B	214	48.433	-3.289	-16.697	1.00	48.72	B	C
ATOM	3337	CE	LYS	B	214	47.295	-2.455	-17.247	1.00	50.58	B	C
ATOM	3338	NZ	LYS	B	214	46.820	-1.443	-16.252	1.00	51.87	B	N
ATOM	3339	C	LYS	B	214	44.897	-6.073	-14.457	1.00	45.57	B	C
ATOM	3340	O	LYS	B	214	44.900	-7.281	-14.681	1.00	45.30	B	O
ATOM	3341	N	ALA	B	215	43.779	-5.352	-14.421	1.00	46.00	B	N
ATOM	3342	CA	ALA	B	215	42.475	-5.959	-14.646	1.00	46.04	B	C
ATOM	3343	CB	ALA	B	215	41.435	-4.878	-14.911	1.00	45.28	B	C
ATOM	3344	C	ALA	B	215	42.558	-6.912	-15.834	1.00	46.64	B	C
ATOM	3345	O	ALA	B	215	41.902	-7.959	-15.860	1.00	46.49	B	O
ATOM	3346	N	ALA	B	216	43.396	-6.545	-16.799	1.00	46.60	B	N
ATOM	3347	CA	ALA	B	216	43.588	-7.325	-18.020	1.00	46.13	B	C
ATOM	3348	CB	ALA	B	216	44.494	-6.550	-18.972	1.00	47.03	B	C
ATOM	3349	C	ALA	B	216	44.148	-8.735	-17.815	1.00	45.76	B	C
ATOM	3350	O	ALA	B	216	43.642	-9.704	-18.395	1.00	46.14	B	O
ATOM	3351	N	SER	B	217	45.190	-8.861	-17.004	1.00	44.20	B	N
ATOM	3352	CA	SER	B	217	45.787	-10.175	-16.791	1.00	44.20	B	C
ATOM	3353	CB	SER	B	217	47.286	-10.102	-17.084	1.00	45.35	B	C
ATOM	3354	OG	SER	B	217	47.878	-9.010	-16.400	1.00	46.68	B	O
ATOM	3355	C	SER	B	217	45.563	-10.767	-15.402	1.00	42.81	B	C
ATOM	3356	O	SER	B	217	46.309	-11.646	-14.961	1.00	42.42	B	O
ATOM	3357	N	ALA	B	218	44.526	-10.298	-14.719	1.00	41.23	B	N
ATOM	3358	CA	ALA	B	218	44.233	-10.777	-13.374	1.00	39.67	B	C
ATOM	3359	CB	ALA	B	218	43.355	-9.765	-12.648	1.00	39.24	B	C
ATOM	3360	C	ALA	B	218	43.568	-12.153	-13.366	1.00	38.42	B	C
ATOM	3361	O	ALA	B	218	44.071	-13.084	-12.733	1.00	38.19	B	O
ATOM	3362	N	ALA	B	219	42.441	-12.271	-14.069	1.00	36.87	B	N
ATOM	3363	CA	ALA	B	219	41.697	-13.528	-14.141	1.00	36.54	B	C

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ATOM	3364	CB	ALA	B	219	40.546	-13.405	-15.141	1.00	34.62	B	C
ATOM	3365	C	ALA	B	219	42.592	-14.700	-14.517	1.00	35.47	B	C
ATOM	3366	O	ALA	B	219	42.415	-15.799	-14.011	1.00	35.45	B	O
ATOM	3367	N	GLU	B	220	43.552	-14.457	-15.402	1.00	37.32	B	N
ATOM	3368	CA	GLU	B	220	44.493	-15.494	-15.848	1.00	38.17	B	C
ATOM	3369	CB	GLU	B	220	45.341	-14.977	-17.013	1.00	41.86	B	C
ATOM	3370	CG	GLU	B	220	44.585	-14.718	-18.317	1.00	47.74	B	C
ATOM	3371	CD	GLU	B	220	45.464	-14.026	-19.357	1.00	50.73	B	C
ATOM	3372	OE1	GLU	B	220	45.954	-12.910	-19.057	1.00	52.06	B	O
ATOM	3373	OE2	GLU	B	220	45.667	-14.589	-20.469	1.00	52.43	B	O
ATOM	3374	C	GLU	B	220	45.439	-15.956	-14.733	1.00	36.23	B	C
ATOM	3375	O	GLU	B	220	45.719	-17.153	-14.604	1.00	35.65	B	O
ATOM	3376	N	LEU	B	221	45.954	-15.006	-13.952	1.00	33.56	B	N
ATOM	3377	CA	LEU	B	221	46.872	-15.326	-12.858	1.00	31.50	B	C
ATOM	3378	CB	LEU	B	221	47.628	-14.068	-12.414	1.00	32.75	B	C
ATOM	3379	CG	LEU	B	221	48.709	-13.481	-13.332	1.00	32.49	B	C
ATOM	3380	CD1	LEU	B	221	48.812	-11.965	-13.141	1.00	32.06	B	C
ATOM	3381	CD2	LEU	B	221	50.031	-14.148	-13.022	1.00	32.00	B	C
ATOM	3382	C	LEU	B	221	46.144	-15.925	-11.654	1.00	29.71	B	C
ATOM	3383	O	LEU	B	221	46.577	-16.941	-11.097	1.00	28.96	B	O
ATOM	3384	N	PHE	B	222	45.044	-15.293	-11.252	1.00	28.59	B	N
ATOM	3385	CA	PHE	B	222	44.279	-15.769	-10.102	1.00	29.46	B	C
ATOM	3386	CB	PHE	B	222	43.212	-14.740	-9.701	1.00	30.15	B	C
ATOM	3387	CG	PHE	B	222	43.772	-13.383	-9.309	1.00	31.40	B	C
ATOM	3388	CD1	PHE	B	222	45.139	-13.205	-9.083	1.00	30.79	B	C
ATOM	3389	CD2	PHE	B	222	42.924	-12.287	-9.150	1.00	31.09	B	C
ATOM	3390	CE1	PHE	B	222	45.651	-11.962	-8.706	1.00	29.88	B	C
ATOM	3391	CE2	PHE	B	222	43.430	-11.043	-8.770	1.00	29.87	B	C
ATOM	3392	CZ	PHE	B	222	44.797	-10.884	-8.549	1.00	30.36	B	C
ATOM	3393	C	PHE	B	222	43.624	-17.119	-10.392	1.00	30.54	B	C
ATOM	3394	O	PHE	B	222	43.213	-17.840	-9.477	1.00	29.61	B	O
ATOM	3395	N	GLY	B	223	43.542	-17.459	-11.674	1.00	31.13	B	N
ATOM	3396	CA	GLY	B	223	42.950	-18.723	-12.062	1.00	31.39	B	C
ATOM	3397	C	GLY	B	223	43.835	-19.901	-11.708	1.00	30.53	B	C
ATOM	3398	O	GLY	B	223	43.356	-21.022	-11.614	1.00	32.45	B	O
ATOM	3399	N	MET	B	224	45.126	-19.656	-11.501	1.00	29.21	B	N
ATOM	3400	CA	MET	B	224	46.048	-20.731	-11.155	1.00	26.79	B	C
ATOM	3401	CB	MET	B	224	47.496	-20.254	-11.294	1.00	25.00	B	C
ATOM	3402	CG	MET	B	224	47.869	-19.867	-12.724	1.00	26.26	B	C
ATOM	3403	SD	MET	B	224	47.701	-21.219	-13.943	1.00	23.16	B	S
ATOM	3404	CE	MET	B	224	49.298	-21.693	-14.085	1.00	20.92	B	C
ATOM	3405	C	MET	B	224	45.780	-21.257	-9.745	1.00	25.66	B	C
ATOM	3406	O	MET	B	224	45.493	-20.492	-8.826	1.00	26.03	B	O
ATOM	3407	N	PRO	B	225	45.890	-22.582	-9.559	1.00	24.22	B	N
ATOM	3408	CD	PRO	B	225	46.473	-23.529	-10.528	1.00	22.50	B	C
ATOM	3409	CA	PRO	B	225	45.652	-23.236	-8.266	1.00	24.99	B	C
ATOM	3410	CB	PRO	B	225	45.914	-24.715	-8.572	1.00	24.75	B	C
ATOM	3411	CG	PRO	B	225	46.975	-24.650	-9.632	1.00	25.68	B	C
ATOM	3412	C	PRO	B	225	46.454	-22.744	-7.051	1.00	25.52	B	C
ATOM	3413	O	PRO	B	225	45.902	-22.629	-5.965	1.00	25.15	B	O
ATOM	3414	N	ASP	B	226	47.741	-22.458	-7.223	1.00	25.22	B	N
ATOM	3415	CA	ASP	B	226	48.549	-22.016	-6.094	1.00	24.62	B	C
ATOM	3416	CB	ASP	B	226	49.905	-22.725	-6.127	1.00	24.63	B	C
ATOM	3417	CG	ASP	B	226	49.779	-24.209	-5.820	1.00	27.92	B	C
ATOM	3418	OD1	ASP	B	226	49.573	-24.560	-4.636	1.00	28.50	B	O
ATOM	3419	OD2	ASP	B	226	49.857	-25.029	-6.761	1.00	27.38	B	O
ATOM	3420	C	ASP	B	226	48.724	-20.506	-5.984	1.00	24.17	B	C
ATOM	3421	O	ASP	B	226	49.562	-20.023	-5.220	1.00	24.42	B	O
ATOM	3422	N	ILE	B	227	47.921	-19.767	-6.739	1.00	24.15	B	N
ATOM	3423	CA	ILE	B	227	47.957	-18.308	-6.703	1.00	24.90	B	C
ATOM	3424	CB	ILE	B	227	48.120	-17.691	-8.106	1.00	24.11	B	C
ATOM	3425	CG2	ILE	B	227	47.932	-16.184	-8.038	1.00	22.64	B	C
ATOM	3426	CG1	ILE	B	227	49.510	-18.026	-8.663	1.00	23.49	B	C
ATOM	3427	CD1	ILE	B	227	49.810	-17.387	-10.014	1.00	23.02	B	C
ATOM	3428	C	ILE	B	227	46.630	-17.891	-6.101	1.00	25.85	B	C
ATOM	3429	O	ILE	B	227	45.577	-18.014	-6.734	1.00	26.12	B	O

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ATOM	3430	N	ASP	B	228	46.694	-17.402	-4.866	1.00	26.77	B	N
ATOM	3431	CA	ASP	B	228	45.507	-17.015	-4.122	1.00	27.18	B	C
ATOM	3432	CB	ASP	B	228	45.700	-17.400	-2.654	1.00	25.65	B	C
ATOM	3433	CG	ASP	B	228	45.994	-18.887	-2.476	1.00	28.75	B	C
ATOM	3434	OD1	ASP	B	228	47.011	-19.231	-1.825	1.00	29.36	B	O
ATOM	3435	OD2	ASP	B	228	45.207	-19.720	-2.985	1.00	28.56	B	O
ATOM	3436	C	ASP	B	228	45.114	-15.548	-4.234	1.00	27.72	B	C
ATOM	3437	O	ASP	B	228	44.296	-15.060	-3.464	1.00	29.05	B	O
ATOM	3438	N	GLY	B	229	45.679	-14.846	-5.202	1.00	26.69	B	N
ATOM	3439	CA	GLY	B	229	45.331	-13.449	-5.355	1.00	26.66	B	C
ATOM	3440	C	GLY	B	229	46.560	-12.640	-5.682	1.00	27.08	B	C
ATOM	3441	O	GLY	B	229	47.534	-13.164	-6.226	1.00	27.13	B	O
ATOM	3442	N	GLY	B	230	46.536	-11.362	-5.339	1.00	26.39	B	N
ATOM	3443	CA	GLY	B	230	47.686	-10.552	-5.645	1.00	26.47	B	C
ATOM	3444	C	GLY	B	230	47.954	-9.382	-4.736	1.00	27.08	B	C
ATOM	3445	O	GLY	B	230	47.112	-8.951	-3.949	1.00	26.31	B	O
ATOM	3446	N	LEU	B	231	49.175	-8.886	-4.844	1.00	26.27	B	N
ATOM	3447	CA	LEU	B	231	49.595	-7.728	-4.088	1.00	28.33	B	C
ATOM	3448	CB	LEU	B	231	50.936	-7.989	-3.397	1.00	25.37	B	C
ATOM	3449	CG	LEU	B	231	51.443	-6.777	-2.612	1.00	24.62	B	C
ATOM	3450	CD1	LEU	B	231	50.422	-6.398	-1.543	1.00	21.36	B	C
ATOM	3451	CD2	LEU	B	231	52.791	-7.097	-1.995	1.00	23.54	B	C
ATOM	3452	C	LEU	B	231	49.741	-6.689	-5.192	1.00	27.68	B	C
ATOM	3453	O	LEU	B	231	50.755	-6.645	-5.881	1.00	28.70	B	O
ATOM	3454	N	VAL	B	232	48.711	-5.874	-5.373	1.00	28.03	B	N
ATOM	3455	CA	VAL	B	232	48.712	-4.879	-6.435	1.00	28.26	B	C
ATOM	3456	CB	VAL	B	232	47.262	-4.487	-6.813	1.00	28.04	B	C
ATOM	3457	CG1	VAL	B	232	47.265	-3.612	-8.057	1.00	28.69	B	C
ATOM	3458	CG2	VAL	B	232	46.441	-5.731	-7.053	1.00	29.01	B	C
ATOM	3459	C	VAL	B	232	49.506	-3.611	-6.135	1.00	29.08	B	C
ATOM	3460	O	VAL	B	232	49.399	-3.028	-5.055	1.00	30.18	B	O
ATOM	3461	N	GLY	B	233	50.296	-3.190	-7.114	1.00	28.95	B	N
ATOM	3462	CA	GLY	B	233	51.094	-1.993	-6.968	1.00	29.21	B	C
ATOM	3463	C	GLY	B	233	50.385	-0.767	-7.521	1.00	29.23	B	C
ATOM	3464	O	GLY	B	233	49.376	-0.313	-6.969	1.00	28.58	B	O
ATOM	3465	N	GLY	B	234	50.904	-0.246	-8.628	1.00	29.54	B	N
ATOM	3466	CA	GLY	B	234	50.335	0.944	-9.241	1.00	30.30	B	C
ATOM	3467	C	GLY	B	234	48.837	0.934	-9.483	1.00	31.55	B	C
ATOM	3468	O	GLY	B	234	48.154	1.930	-9.230	1.00	31.14	B	O
ATOM	3469	N	ALA	B	235	48.319	-0.189	-9.964	1.00	30.91	B	N
ATOM	3470	CA	ALA	B	235	46.896	-0.304	-10.269	1.00	31.05	B	C
ATOM	3471	CB	ALA	B	235	46.587	-1.713	-10.768	1.00	30.62	B	C
ATOM	3472	C	ALA	B	235	45.984	0.051	-9.096	1.00	31.08	B	C
ATOM	3473	O	ALA	B	235	44.871	0.539	-9.298	1.00	30.40	B	O
ATOM	3474	N	SER	B	236	46.460	-0.178	-7.873	1.00	31.28	B	N
ATOM	3475	CA	SER	B	236	45.671	0.101	-6.672	1.00	31.64	B	C
ATOM	3476	CB	SER	B	236	46.358	-0.497	-5.439	1.00	32.56	B	C
ATOM	3477	OG	SER	B	236	47.642	0.070	-5.242	1.00	32.73	B	O
ATOM	3478	C	SER	B	236	45.397	1.582	-6.418	1.00	31.55	B	C
ATOM	3479	O	SER	B	236	44.661	1.929	-5.502	1.00	31.79	B	O
ATOM	3480	N	LEU	B	237	45.995	2.455	-7.218	1.00	32.34	B	N
ATOM	3481	CA	LEU	B	237	45.788	3.888	-7.062	1.00	33.53	B	C
ATOM	3482	CB	LEU	B	237	47.031	4.641	-7.550	1.00	31.66	B	C
ATOM	3483	CG	LEU	B	237	48.294	4.294	-6.748	1.00	32.78	B	C
ATOM	3484	CD1	LEU	B	237	49.545	4.874	-7.409	1.00	30.55	B	C
ATOM	3485	CD2	LEU	B	237	48.135	4.820	-5.334	1.00	29.80	B	C
ATOM	3486	C	LEU	B	237	44.547	4.324	-7.854	1.00	34.47	B	C
ATOM	3487	O	LEU	B	237	44.270	5.517	-7.983	1.00	34.77	B	O
ATOM	3488	N	ASN	B	238	43.809	3.346	-8.377	1.00	33.75	B	N
ATOM	3489	CA	ASN	B	238	42.603	3.616	-9.148	1.00	34.93	B	C
ATOM	3490	CB	ASN	B	238	42.880	3.403	-10.631	1.00	35.53	B	C
ATOM	3491	CG	ASN	B	238	41.723	3.839	-11.508	1.00	36.01	B	C
ATOM	3492	OD1	ASN	B	238	40.701	3.149	-11.618	1.00	34.98	B	O
ATOM	3493	ND2	ASN	B	238	41.872	5.000	-12.130	1.00	36.35	B	N
ATOM	3494	C	ASN	B	238	41.439	2.722	-8.713	1.00	35.91	B	C
ATOM	3495	O	ASN	B	238	41.423	1.519	-8.979	1.00	35.73	B	O

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ATOM	3496	N	ALA	B	239	40.465	3.316	-8.038	1.00	37.26	B	N
ATOM	3497	CA	ALA	B	239	39.300	2.579	-7.563	1.00	38.65	B	C
ATOM	3498	CB	ALA	B	239	38.200	3.560	-7.175	1.00	38.08	B	C
ATOM	3499	C	ALA	B	239	38.779	1.598	-8.613	1.00	39.50	B	C
ATOM	3500	O	ALA	B	239	38.491	0.442	-8.306	1.00	38.78	B	O
ATOM	3501	N	ASP	B	240	38.674	2.069	-9.855	1.00	41.17	B	N
ATOM	3502	CA	ASP	B	240	38.166	1.259	-10.963	1.00	42.15	B	C
ATOM	3503	CB	ASP	B	240	37.890	2.156	-12.179	1.00	44.74	B	C
ATOM	3504	CG	ASP	B	240	36.657	3.035	-11.986	1.00	48.20	B	C
ATOM	3505	OD1	ASP	B	240	36.191	3.166	-10.828	1.00	49.48	B	O
ATOM	3506	OD2	ASP	B	240	36.156	3.601	-12.989	1.00	49.33	B	O
ATOM	3507	C	ASP	B	240	39.045	0.079	-11.385	1.00	41.03	B	C
ATOM	3508	O	ASP	B	240	38.544	-1.032	-11.535	1.00	40.18	B	O
ATOM	3509	N	GLU	B	241	40.339	0.297	-11.600	1.00	39.81	B	N
ATOM	3510	CA	GLU	B	241	41.160	-0.834	-11.992	1.00	40.30	B	C
ATOM	3511	CB	GLU	B	241	42.555	-0.404	-12.448	1.00	41.71	B	C
ATOM	3512	CG	GLU	B	241	43.113	-1.385	-13.478	1.00	45.04	B	C
ATOM	3513	CD	GLU	B	241	44.566	-1.128	-13.836	1.00	48.38	B	C
ATOM	3514	OE1	GLU	B	241	44.967	0.064	-13.903	1.00	49.79	B	O
ATOM	3515	OE2	GLU	B	241	45.302	-2.124	-14.069	1.00	48.00	B	O
ATOM	3516	C	GLU	B	241	41.283	-1.817	-10.832	1.00	38.72	B	C
ATOM	3517	O	GLU	B	241	41.313	-3.031	-11.041	1.00	39.89	B	O
ATOM	3518	N	PHE	B	242	41.339	-1.292	-9.611	1.00	36.56	B	N
ATOM	3519	CA	PHE	B	242	41.457	-2.130	-8.424	1.00	34.80	B	C
ATOM	3520	CB	PHE	B	242	41.592	-1.259	-7.172	1.00	32.39	B	C
ATOM	3521	CG	PHE	B	242	42.069	-2.012	-5.962	1.00	29.93	B	C
ATOM	3522	CD1	PHE	B	242	43.355	-2.541	-5.923	1.00	29.06	B	C
ATOM	3523	CD2	PHE	B	242	41.227	-2.216	-4.872	1.00	29.78	B	C
ATOM	3524	CE1	PHE	B	242	43.797	-3.262	-4.818	1.00	26.33	B	C
ATOM	3525	CE2	PHE	B	242	41.661	-2.939	-3.764	1.00	28.00	B	C
ATOM	3526	CZ	PHE	B	242	42.951	-3.461	-3.742	1.00	28.48	B	C
ATOM	3527	C	PHE	B	242	40.246	-3.048	-8.269	1.00	34.98	B	C
ATOM	3528	O	PHE	B	242	40.388	-4.253	-8.043	1.00	34.42	B	O
ATOM	3529	N	GLY	B	243	39.051	-2.471	-8.375	1.00	34.52	B	N
ATOM	3530	CA	GLY	B	243	37.843	-3.259	-8.244	1.00	33.64	B	C
ATOM	3531	C	GLY	B	243	37.780	-4.362	-9.285	1.00	33.97	B	C
ATOM	3532	O	GLY	B	243	37.322	-5.466	-9.004	1.00	34.21	B	O
ATOM	3533	N	ALA	B	244	38.239	-4.065	-10.494	1.00	33.47	B	N
ATOM	3534	CA	ALA	B	244	38.225	-5.051	-11.559	1.00	34.60	B	C
ATOM	3535	CB	ALA	B	244	38.714	-4.428	-12.850	1.00	34.04	B	C
ATOM	3536	C	ALA	B	244	39.137	-6.199	-11.142	1.00	35.55	B	C
ATOM	3537	O	ALA	B	244	38.825	-7.370	-11.359	1.00	34.72	B	O
ATOM	3538	N	ILE	B	245	40.268	-5.869	-10.530	1.00	35.91	B	N
ATOM	3539	CA	ILE	B	245	41.172	-6.920	-10.098	1.00	36.74	B	C
ATOM	3540	CB	ILE	B	245	42.512	-6.347	-9.585	1.00	36.73	B	C
ATOM	3541	CG2	ILE	B	245	43.411	-7.487	-9.110	1.00	35.81	B	C
ATOM	3542	CG1	ILE	B	245	43.188	-5.549	-10.709	1.00	36.80	B	C
ATOM	3543	CD1	ILE	B	245	44.572	-5.032	-10.371	1.00	37.65	B	C
ATOM	3544	C	ILE	B	245	40.511	-7.746	-9.000	1.00	36.45	B	C
ATOM	3545	O	ILE	B	245	40.536	-8.980	-9.033	1.00	37.06	B	O
ATOM	3546	N	CYS	B	246	39.901	-7.075	-8.031	1.00	36.49	B	N
ATOM	3547	CA	CYS	B	246	39.249	-7.794	-6.945	1.00	36.70	B	C
ATOM	3548	CB	CYS	B	246	38.591	-6.810	-5.967	1.00	36.52	B	C
ATOM	3549	SG	CYS	B	246	39.775	-5.752	-5.061	1.00	36.03	B	S
ATOM	3550	C	CYS	B	246	38.208	-8.761	-7.502	1.00	37.42	B	C
ATOM	3551	O	CYS	B	246	38.153	-9.929	-7.113	1.00	37.10	B	O
ATOM	3552	N	ARG	B	247	37.383	-8.285	-8.425	1.00	37.90	B	N
ATOM	3553	CA	ARG	B	247	36.366	-9.154	-8.990	1.00	37.95	B	C
ATOM	3554	CB	ARG	B	247	35.443	-8.372	-9.929	1.00	39.58	B	C
ATOM	3555	CG	ARG	B	247	34.298	-7.691	-9.181	1.00	40.37	B	C
ATOM	3556	CD	ARG	B	247	33.245	-7.105	-10.120	1.00	41.08	B	C
ATOM	3557	NE	ARG	B	247	33.546	-5.724	-10.498	1.00	43.82	B	N
ATOM	3558	CZ	ARG	B	247	34.356	-5.370	-11.491	1.00	44.79	B	C
ATOM	3559	NH1	ARG	B	247	34.954	-6.305	-12.222	1.00	45.37	B	N
ATOM	3560	NH2	ARG	B	247	34.565	-4.075	-11.758	1.00	44.12	B	N
ATOM	3561	C	ARG	B	247	37.009	-10.327	-9.710	1.00	37.05	B	C

FIGURE 9 - 54

ATOM	3562	O	ARG	B	247	36.510	-11.450	-9.639	1.00	36.84	B	O
ATOM	3563	N	ALA	B	248	38.125	-10.080	-10.381	1.00	35.08	B	N
ATOM	3564	CA	ALA	B	248	38.804	-11.150	-11.090	1.00	35.84	B	C
ATOM	3565	CB	ALA	B	248	40.084	-10.640	-11.727	1.00	33.58	B	C
ATOM	3566	C	ALA	B	248	39.116	-12.292	-10.136	1.00	35.80	B	C
ATOM	3567	O	ALA	B	248	39.158	-13.444	-10.542	1.00	37.62	B	O
ATOM	3568	N	ALA	B	249	39.315	-11.978	-8.862	1.00	35.64	B	N
ATOM	3569	CA	ALA	B	249	39.631	-13.006	-7.878	1.00	36.31	B	C
ATOM	3570	CB	ALA	B	249	40.381	-12.380	-6.704	1.00	33.52	B	C
ATOM	3571	C	ALA	B	249	38.411	-13.769	-7.360	1.00	37.06	B	C
ATOM	3572	O	ALA	B	249	38.549	-14.793	-6.702	1.00	36.02	B	O
ATOM	3573	N	GLY	B	250	37.217	-13.273	-7.650	1.00	39.46	B	N
ATOM	3574	CA	GLY	B	250	36.026	-13.944	-7.164	1.00	42.33	B	C
ATOM	3575	C	GLY	B	250	35.567	-15.111	-8.014	1.00	44.29	B	C
ATOM	3576	O	GLY	B	250	34.335	-15.230	-8.226	1.00	45.84	B	O
ATOM	3577	OXT	GLY	B	250	36.427	-15.917	-8.448	1.00	44.68	B	O
TER	3578		GLY	B	250						B	
ATOM	3579	OH2	WAT		1	63.739	13.680	3.442	1.00	21.18	S	
ATOM	3580	OH2	WAT		2	46.539	11.585	11.681	1.00	18.96	S	
ATOM	3581	OH2	WAT		3	43.567	-19.385	-7.432	1.00	25.91	S	
ATOM	3582	OH2	WAT		4	71.012	30.393	25.191	1.00	32.51	S	
ATOM	3583	OH2	WAT		5	75.981	26.094	0.757	1.00	20.73	S	
ATOM	3584	OH2	WAT		6	48.777	11.393	9.884	1.00	22.78	S	
ATOM	3585	OH2	WAT		7	56.505	-5.204	12.895	1.00	19.66	S	
ATOM	3586	OH2	WAT		8	59.027	10.900	23.449	1.00	22.67	S	
ATOM	3587	OH2	WAT		9	53.790	-3.883	-4.465	1.00	19.70	S	
ATOM	3588	OH2	WAT		10	55.768	-13.300	17.134	1.00	24.11	S	
ATOM	3589	OH2	WAT		11	55.028	18.137	22.898	1.00	25.58	S	
ATOM	3590	OH2	WAT		12	72.703	11.819	16.372	1.00	22.99	S	
ATOM	3591	OH2	WAT		13	49.271	16.075	28.292	1.00	27.82	S	
ATOM	3592	OH2	WAT		14	45.485	10.010	8.553	1.00	25.65	S	
ATOM	3593	OH2	WAT		15	59.531	-0.501	22.088	1.00	32.02	S	
ATOM	3594	OH2	WAT		16	56.843	11.447	12.086	1.00	26.98	S	
ATOM	3595	OH2	WAT		17	61.865	0.446	9.105	1.00	25.39	S	
ATOM	3596	OH2	WAT		18	58.552	-3.361	22.182	1.00	21.78	S	
ATOM	3597	OH2	WAT		19	82.120	18.194	26.672	1.00	27.91	S	
ATOM	3598	OH2	WAT		20	46.996	-16.906	5.047	1.00	31.56	S	
ATOM	3599	OH2	WAT		21	57.610	-4.027	3.628	1.00	23.68	S	
ATOM	3600	OH2	WAT		22	52.890	-0.095	23.500	1.00	32.40	S	
ATOM	3601	OH2	WAT		23	47.078	8.133	9.748	1.00	25.02	S	
ATOM	3602	OH2	WAT		24	65.725	10.982	12.443	1.00	21.03	S	
ATOM	3603	OH2	WAT		25	68.888	27.520	12.697	1.00	30.16	S	
ATOM	3604	OH2	WAT		26	72.959	24.629	-0.833	1.00	28.76	S	
ATOM	3605	OH2	WAT		27	64.407	24.946	34.919	1.00	30.03	S	
ATOM	3606	OH2	WAT		28	82.109	28.612	19.089	1.00	25.80	S	
ATOM	3607	OH2	WAT		29	59.333	24.901	6.708	1.00	29.91	S	
ATOM	3608	OH2	WAT		30	60.572	-8.956	-1.830	1.00	24.69	S	
ATOM	3609	OH2	WAT		31	71.583	13.346	28.698	1.00	31.02	S	
ATOM	3610	OH2	WAT		32	81.021	32.930	13.694	1.00	37.30	S	
ATOM	3611	OH2	WAT		33	50.899	12.898	29.572	1.00	30.82	S	
ATOM	3612	OH2	WAT		34	42.795	14.907	18.385	1.00	28.46	S	
ATOM	3613	OH2	WAT		35	75.426	12.778	9.279	1.00	29.79	S	
ATOM	3614	OH2	WAT		36	53.891	23.103	10.722	1.00	26.52	S	
ATOM	3615	OH2	WAT		37	43.505	0.281	-3.618	1.00	32.25	S	
ATOM	3616	OH2	WAT		38	51.056	11.344	25.909	1.00	34.32	S	
ATOM	3617	OH2	WAT		39	63.457	5.623	6.569	1.00	26.78	S	
ATOM	3618	OH2	WAT		40	42.887	5.137	21.307	1.00	36.91	S	
ATOM	3619	OH2	WAT		41	63.977	6.391	2.587	1.00	31.27	S	
ATOM	3620	OH2	WAT		42	62.463	-0.901	12.868	1.00	26.15	S	
ATOM	3621	OH2	WAT		43	63.052	-9.913	-2.660	1.00	31.73	S	
ATOM	3622	OH2	WAT		44	84.960	22.849	9.750	1.00	32.28	S	
ATOM	3623	OH2	WAT		45	53.936	6.657	12.882	1.00	36.99	S	
ATOM	3624	OH2	WAT		46	66.545	30.127	26.084	1.00	34.75	S	
ATOM	3625	OH2	WAT		47	83.758	32.772	7.138	1.00	31.70	S	
ATOM	3626	OH2	WAT		48	55.487	14.405	-4.745	1.00	27.79	S	
ATOM	3627	OH2	WAT		49	68.567	19.860	-1.275	1.00	25.45	S	

FIGURE 9 - 55

ATOM	3628	OH2	WAT	50	35.299	-8.627	-1.566	1.00	37.22	S
ATOM	3629	OH2	WAT	51	75.282	7.386	10.848	1.00	28.73	S
ATOM	3630	OH2	WAT	52	47.602	21.845	29.388	1.00	36.21	S
ATOM	3631	OH2	WAT	53	56.100	29.843	22.330	1.00	29.84	S
ATOM	3632	OH2	WAT	54	70.307	21.808	33.869	1.00	35.11	S
ATOM	3633	OH2	WAT	55	51.842	2.180	5.586	1.00	27.16	S
ATOM	3634	OH2	WAT	56	49.428	18.363	30.767	1.00	34.50	S
ATOM	3635	OH2	WAT	57	52.432	-26.252	-10.500	1.00	31.73	S
ATOM	3636	OH2	WAT	58	88.006	14.325	18.106	1.00	38.40	S
ATOM	3637	OH2	WAT	59	56.307	28.467	17.331	1.00	35.26	S
ATOM	3638	OH2	WAT	60	72.612	30.570	9.885	1.00	30.94	S
ATOM	3639	OH2	WAT	61	59.289	-25.133	11.886	1.00	36.57	S
ATOM	3640	OH2	WAT	62	62.849	-12.930	4.372	1.00	34.28	S
ATOM	3641	OH2	WAT	63	48.208	11.640	26.364	1.00	31.54	S
ATOM	3642	OH2	WAT	64	57.116	-25.895	-8.962	1.00	28.63	S
ATOM	3643	OH2	WAT	65	57.543	3.069	8.138	1.00	36.57	S
ATOM	3644	OH2	WAT	66	51.001	2.103	-5.920	1.00	27.74	S
ATOM	3645	OH2	WAT	67	61.087	-8.616	16.804	1.00	33.04	S
ATOM	3646	OH2	WAT	68	66.425	-6.837	-11.132	1.00	39.35	S
ATOM	3647	OH2	WAT	69	77.598	22.382	34.696	1.00	34.40	S
ATOM	3648	OH2	WAT	70	54.065	4.324	5.269	1.00	32.40	S
ATOM	3649	OH2	WAT	71	48.065	-21.741	7.107	1.00	28.43	S
ATOM	3650	OH2	WAT	72	77.492	32.093	20.572	1.00	32.41	S
ATOM	3651	OH2	WAT	73	67.956	17.031	32.792	1.00	38.47	S
ATOM	3652	OH2	WAT	74	35.792	-1.645	-11.357	1.00	41.03	S
ATOM	3653	OH2	WAT	75	72.097	31.059	22.915	1.00	31.39	S
ATOM	3654	OH2	WAT	76	60.828	-5.551	5.997	1.00	35.88	S
ATOM	3655	OH2	WAT	77	86.099	14.188	11.173	1.00	36.28	S
ATOM	3656	OH2	WAT	78	74.845	10.187	16.911	1.00	30.97	S
ATOM	3657	OH2	WAT	79	50.465	32.604	25.734	1.00	35.32	S
ATOM	3658	OH2	WAT	80	42.236	-11.831	5.496	1.00	38.33	S
ATOM	3659	OH2	WAT	81	58.627	-4.082	6.362	1.00	34.82	S
ATOM	3660	OH2	WAT	82	67.975	-11.445	-2.979	1.00	36.42	S
ATOM	3661	OH2	WAT	83	45.950	8.709	-4.339	1.00	41.88	S
ATOM	3662	OH2	WAT	84	66.646	16.717	-3.564	1.00	38.92	S
ATOM	3663	OH2	WAT	85	76.878	19.131	-4.499	1.00	30.97	S
ATOM	3664	OH2	WAT	86	68.904	30.992	21.253	1.00	28.40	S
ATOM	3665	OH2	WAT	87	78.208	8.520	16.860	1.00	28.01	S
ATOM	3666	OH2	WAT	88	54.448	31.296	29.005	1.00	44.80	S
ATOM	3667	OH2	WAT	89	67.347	24.984	35.233	1.00	34.81	S
ATOM	3668	OH2	WAT	90	60.370	-26.116	-2.606	1.00	35.93	S
ATOM	3669	OH2	WAT	91	37.567	1.014	8.342	1.00	33.11	S
ATOM	3670	OH2	WAT	92	65.188	12.783	21.098	1.00	26.41	S
ATOM	3671	OH2	WAT	93	65.456	11.831	23.641	1.00	34.38	S
ATOM	3672	OH2	WAT	94	56.795	-30.673	0.572	1.00	42.38	S
ATOM	3673	OH2	WAT	95	56.901	8.116	12.364	1.00	38.07	S
ATOM	3674	OH2	WAT	96	42.831	16.110	15.976	1.00	34.52	S
ATOM	3675	OH2	WAT	97	42.170	16.768	20.681	1.00	28.67	S
ATOM	3676	OH2	WAT	98	57.637	7.463	14.873	1.00	31.48	S
ATOM	3677	OH2	WAT	99	56.202	35.047	27.703	1.00	32.52	S
ATOM	3678	OH2	WAT	100	41.686	-3.364	9.116	1.00	28.74	S
ATOM	3679	OH2	WAT	101	86.586	3.817	23.769	1.00	41.10	S
ATOM	3680	OH2	WAT	102	58.302	1.697	11.346	1.00	31.83	S
ATOM	3681	OH2	WAT	103	58.832	34.722	27.087	1.00	38.83	S
ATOM	3682	OH2	WAT	104	85.938	9.832	11.193	1.00	46.57	S
ATOM	3683	OH2	WAT	105	41.407	11.430	24.565	1.00	32.31	S
ATOM	3684	OH2	WAT	106	60.136	7.850	5.330	1.00	30.07	S
ATOM	3685	OH2	WAT	107	86.102	28.442	14.054	1.00	34.85	S
ATOM	3686	OH2	WAT	108	53.305	24.445	31.958	1.00	39.87	S
ATOM	3687	OH2	WAT	109	65.921	10.467	9.630	1.00	34.53	S
ATOM	3688	OH2	WAT	110	68.629	4.220	1.225	1.00	45.83	S
ATOM	3689	OH2	WAT	111	68.562	10.278	8.956	1.00	46.62	S
ATOM	3690	OH2	WAT	112	56.017	-15.270	15.035	1.00	36.72	S
ATOM	3691	OH2	WAT	113	59.462	26.860	33.469	1.00	35.19	S
ATOM	3692	OH2	WAT	114	60.433	9.337	-5.622	1.00	26.88	S
ATOM	3693	OH2	WAT	115	66.775	-10.262	0.003	1.00	42.01	S

FIGURE 9 - 56

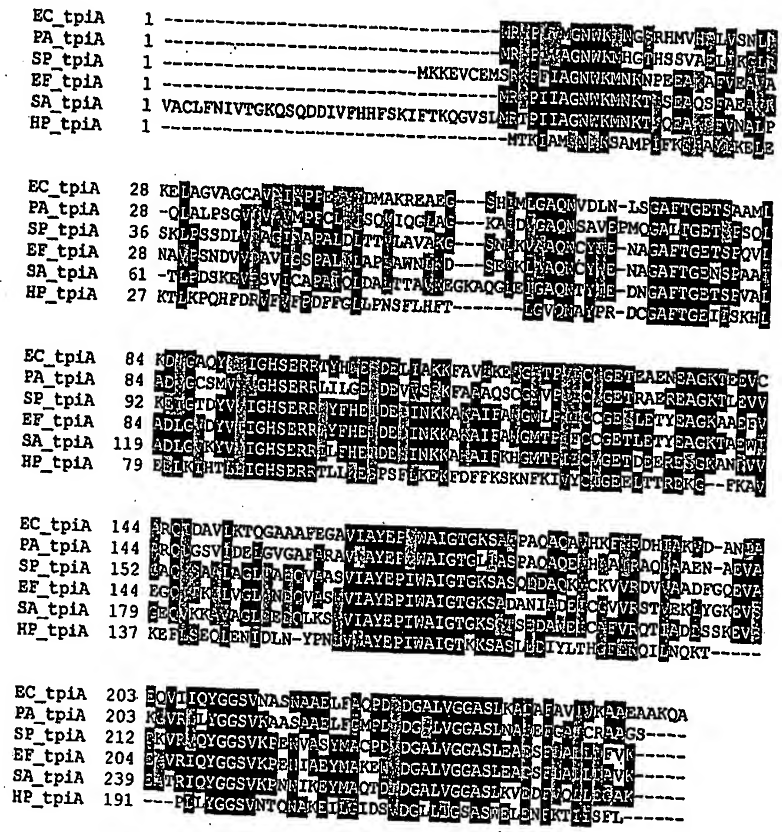
ATOM	3694	OH2	WAT	116	67.236	14.471	21.708	1.00	39.77	S
ATOM	3695	OH2	WAT	117	79.784	3.290	23.426	1.00	38.65	S
ATOM	3696	OH2	WAT	118	57.689	2.771	26.058	1.00	35.29	S
ATOM	3697	OH2	WAT	119	55.846	-24.062	14.597	1.00	40.39	S
ATOM	3698	OH2	WAT	120	70.641	6.345	21.248	1.00	36.46	S
ATOM	3699	OH2	WAT	121	78.813	15.534	34.365	1.00	30.13	S
ATOM	3700	OH2	WAT	122	71.200	16.610	30.358	1.00	42.54	S
ATOM	3701	OH2	WAT	123	70.119	-11.382	7.901	1.00	35.98	S
ATOM	3702	OH2	WAT	124	69.454	7.610	29.487	1.00	45.35	S
ATOM	3703	OH2	WAT	125	66.807	32.983	14.967	1.00	32.20	S
ATOM	3704	OH2	WAT	126	59.180	6.165	-8.206	1.00	32.59	S
ATOM	3705	OH2	WAT	127	67.208	-1.417	10.324	1.00	35.14	S
ATOM	3706	OH2	WAT	128	53.773	-6.675	-5.077	1.00	40.92	S
ATOM	3707	OH2	WAT	129	37.999	9.731	6.178	1.00	37.69	S
ATOM	3708	OH2	WAT	130	70.760	31.115	-1.126	1.00	48.87	S
ATOM	3709	OH2	WAT	131	48.587	15.254	32.305	1.00	42.90	S
ATOM	3710	OH2	WAT	132	46.698	17.046	28.377	1.00	33.90	S
ATOM	3711	OH2	WAT	133	69.756	-10.705	4.417	1.00	40.92	S
ATOM	3712	OH2	WAT	134	61.801	11.765	-5.827	1.00	30.08	S
ATOM	3713	OH2	WAT	135	65.150	33.908	25.255	1.00	40.06	S
ATOM	3714	OH2	WAT	136	64.483	23.992	38.822	1.00	37.47	S
ATOM	3715	OH2	WAT	137	68.996	-15.404	5.846	1.00	43.32	S
ATOM	3716	OH2	WAT	138	81.024	20.065	34.384	1.00	35.58	S
ATOM	3717	OH2	WAT	139	87.308	15.441	20.501	1.00	45.36	S
ATOM	3718	OH2	WAT	140	77.132	5.263	24.102	1.00	38.49	S
ATOM	3719	OH2	WAT	141	36.486	-16.779	-11.072	1.00	38.24	S
ATOM	3720	OH2	WAT	142	84.757	23.777	23.127	1.00	37.17	S
ATOM	3721	OH2	WAT	143	70.264	28.931	10.768	1.00	31.00	S
ATOM	3722	OH2	WAT	144	41.269	-10.622	-16.396	1.00	41.13	S
ATOM	3723	OH2	WAT	145	68.274	7.143	22.602	1.00	46.06	S
ATOM	3724	OH2	WAT	146	62.567	14.392	28.562	1.00	44.69	S
ATOM	3725	OH2	WAT	147	64.731	24.523	4.703	1.00	36.32	S
ATOM	3726	OH2	WAT	148	43.669	-20.914	-5.240	1.00	38.93	S
ATOM	3727	OH2	WAT	149	34.494	14.494	-5.873	1.00	40.21	S
ATOM	3728	OH2	WAT	150	63.549	-12.958	6.999	1.00	32.43	S
ATOM	3729	OH2	WAT	151	59.144	32.488	29.232	1.00	44.36	S
ATOM	3730	OH2	WAT	152	64.594	12.517	7.745	1.00	43.80	S
ATOM	3731	OH2	WAT	153	42.616	-18.758	-3.095	1.00	36.69	S
ATOM	3732	OH2	WAT	154	54.449	4.642	2.609	1.00	38.54	S
ATOM	3733	OH2	WAT	155	50.417	0.550	21.384	1.00	44.81	S
ATOM	3734	OH2	WAT	156	37.279	-8.043	-13.535	1.00	38.19	S
ATOM	3735	OH2	WAT	157	49.298	-13.025	12.873	1.00	37.47	S
ATOM	3736	OH2	WAT	158	41.030	24.450	22.675	1.00	46.89	S
ATOM	3737	OH2	WAT	159	72.495	2.930	6.308	1.00	38.50	S
ATOM	3738	OH2	WAT	160	61.298	27.611	13.565	1.00	46.96	S
ATOM	3739	OH2	WAT	161	62.971	36.604	18.041	1.00	44.82	S
ATOM	3740	OH2	WAT	162	83.572	13.349	29.985	1.00	43.32	S
ATOM	3741	OH2	WAT	163	36.643	10.222	1.115	1.00	29.66	S
ATOM	3742	OH2	WAT	164	57.618	-4.939	-7.098	1.00	41.52	S
ATOM	3743	OH2	WAT	165	77.841	8.652	12.101	1.00	34.90	S
ATOM	3744	OH2	WAT	166	40.961	-15.929	-6.954	1.00	44.03	S
ATOM	3745	OH2	WAT	167	66.564	-9.125	2.563	1.00	36.50	S
ATOM	3746	OH2	WAT	168	57.004	-4.662	8.557	1.00	30.72	S
ATOM	3747	OH2	WAT	169	43.288	-20.287	4.714	1.00	47.63	S
ATOM	3748	OH2	WAT	170	75.464	26.284	35.459	1.00	44.63	S
ATOM	3749	OH2	WAT	171	53.679	5.266	25.380	1.00	45.04	S
ATOM	3750	OH2	WAT	172	56.443	12.148	-7.782	1.00	31.88	S
ATOM	3751	OH2	WAT	173	70.455	-16.383	-1.712	1.00	44.98	S
ATOM	3752	OH2	WAT	174	30.948	-3.393	2.233	1.00	40.95	S
ATOM	3753	OH2	WAT	175	41.711	20.576	18.327	1.00	43.75	S
ATOM	3754	OH2	WAT	176	78.523	5.879	7.675	1.00	42.69	S
ATOM	3755	OH2	WAT	177	38.101	5.062	-10.304	1.00	40.30	S
ATOM	3756	OH2	WAT	178	54.268	29.952	20.197	1.00	35.72	S
ATOM	3757	OH2	WAT	179	72.440	29.012	32.447	1.00	39.75	S
ATOM	3758	OH2	WAT	180	80.516	13.435	32.834	1.00	43.98	S
ATOM	3759	OH2	WAT	181	64.768	1.119	21.506	1.00	43.72	S

FIGURE 9 - 57

ATOM	3760	OH2	WAT	182	86.668	13.793	22.641	1.00	45.55	S
ATOM	3761	OH2	WAT	183	53.783	15.211	-2.617	1.00	41.77	S
ATOM	3762	OH2	WAT	184	47.017	17.986	7.210	1.00	47.29	S
ATOM	3763	OH2	WAT	185	47.776	-19.055	6.655	1.00	47.45	S
ATOM	3764	OH2	WAT	186	61.369	35.933	24.964	1.00	43.41	S
ATOM	3765	OH2	WAT	187	55.247	-3.515	-6.768	1.00	40.64	S
ATOM	3766	OH2	WAT	188	42.534	9.618	-6.369	1.00	39.21	S
ATOM	3767	OH2	WAT	189	55.186	5.737	16.154	1.00	41.22	S
ATOM	3768	OH2	WAT	190	68.693	23.313	36.902	1.00	39.71	S
ATOM	3769	OH2	WAT	191	78.189	7.398	4.865	1.00	47.98	S
ATOM	3770	OH2	WAT	192	45.493	-14.622	6.823	1.00	37.56	S
ATOM	3771	OH2	WAT	193	77.993	11.404	-1.840	1.00	41.99	S
ATOM	3772	OH2	WAT	194	37.218	-19.477	0.511	1.00	47.19	S

FIGURE 9 - 58

FIGURE 10



Organisms are abbreviated as follows: EC = *Eschericia coli*; HP = *Helicobacter pylori*; PA = *Pseudomonas aeruginosa*; SA = *Staphylococcus aureus*; SP = *Streptococcus pneumoniae*; EF = *Enterococcus faecalis*.

FIGURE 11

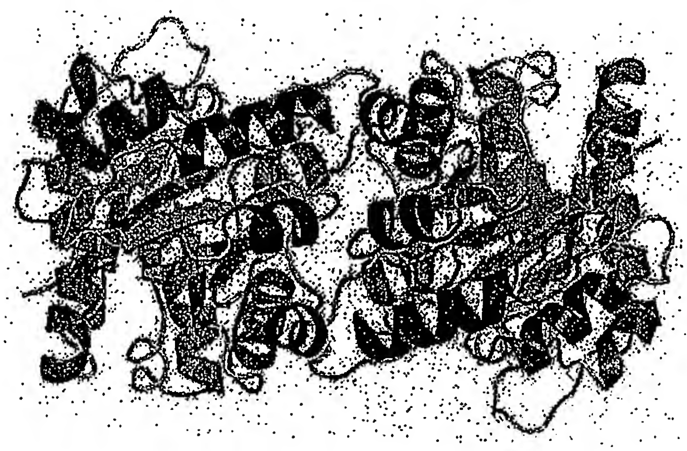


FIGURE 12

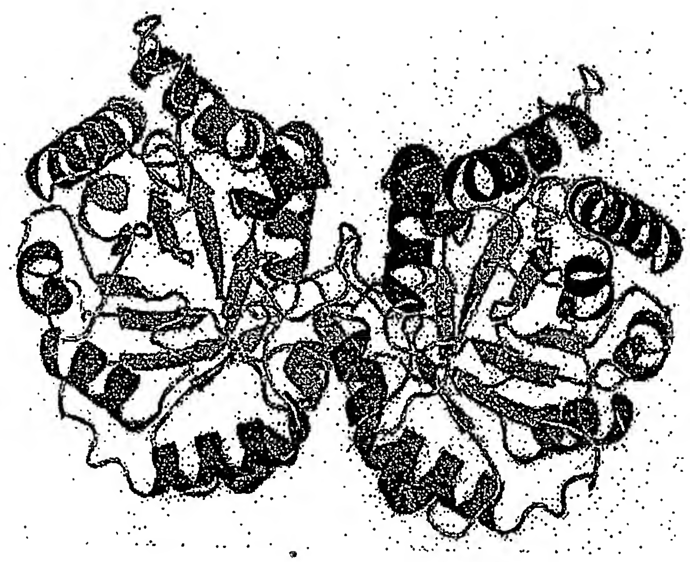


FIGURE 13

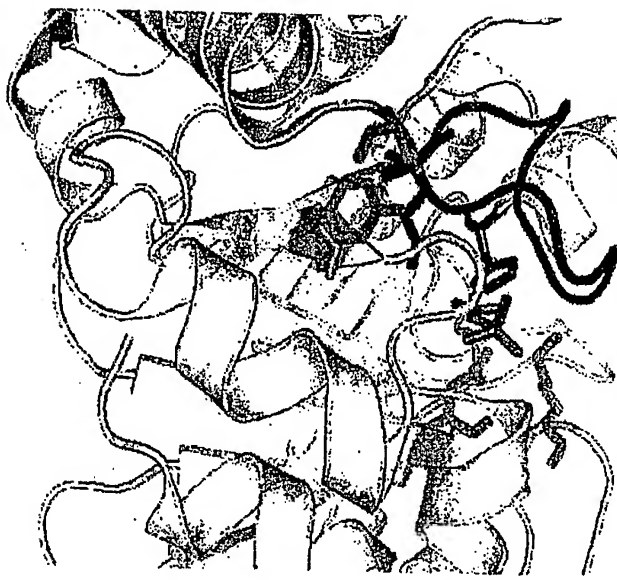


FIGURE 14

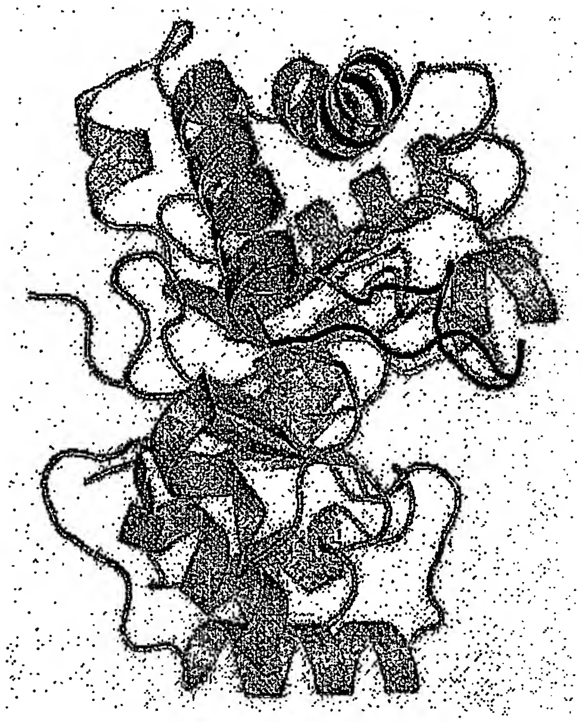


FIGURE 15

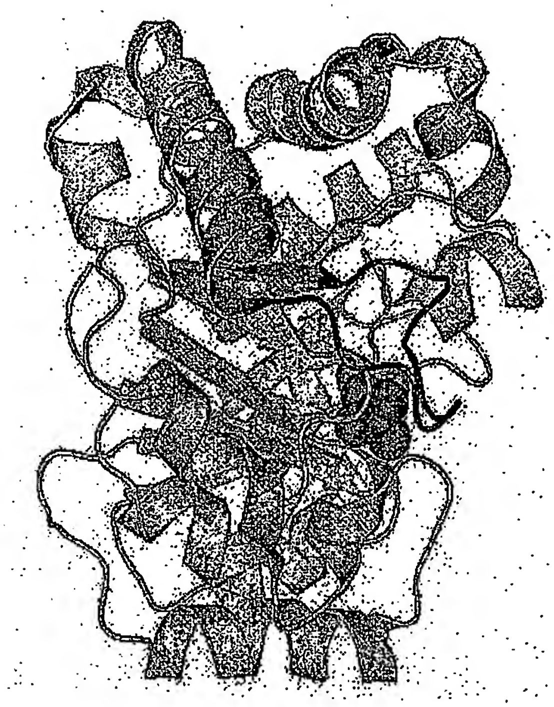


FIGURE 16

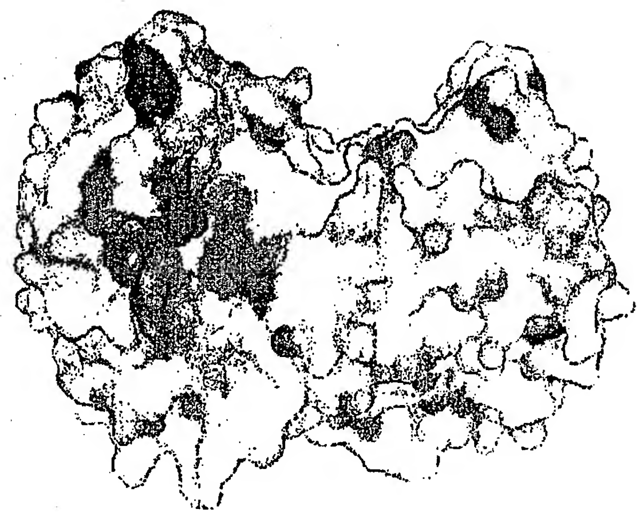
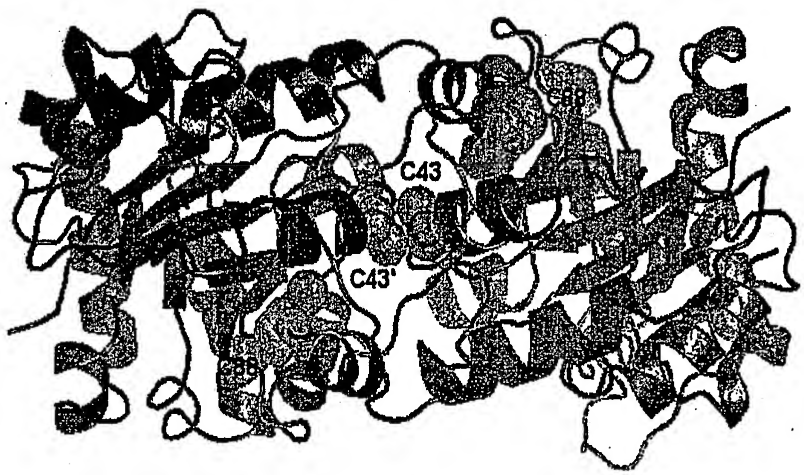


FIGURE 17

TABLE 4: Interface residues of TcTIM, PaTIM, and HsTIM

Tc TIM	Pa TIM	Hs TIM
N12	N9	N11
K14	K11	K13
C15	M12	M14
N16	H13	N15
G17	G14	G16
S18	T15	R17
E19	H16	K18
S20	S17	Q19
T45	P42	P44
F46	C43	T45
L47	L44	A46
H48	F45	Y47
I49	I46	I48
P50	S47	D49
M51	Q48	F50
Q66	Q63	Q64
N67	N64	N65
I69	V67	V67
S72	Q71	N71
G73	G72	G72
A74	A73	A73
F75	L74	F74
T76	T75	T75
G77	G76	G76
E78	E77	E77
V79	T78	I78
S80	A79	S79
I83	Q82	M82
L84	L83	I83
D86	D85	D85
Y87	V86	C86
I89	C88	A88
V93	L92	V92
H96	H95	H95
E98	E97	E97
R99	R98	R98
Y102	I101	V101
Y103	L102	F102
I173	I172	I170
G174	G173	G171

FIGURE 18



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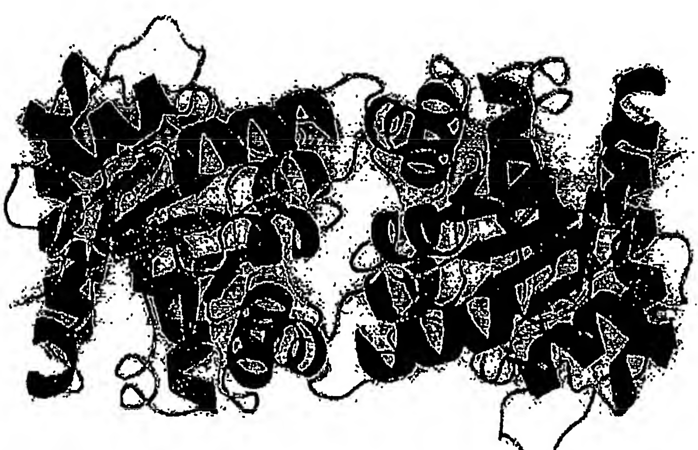
(74) Agent: **BERESKIN & PARR**; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,

[Continued on next page]

(54) Title: PURIFIED POLYPEPTIDES FROM *PSEUDOMONAS AERUGINOSA*



(57) Abstract: The present invention relates to drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

WO 03/027274 A3

TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 2 October 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 02/01453

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/90 C07K14/21 C07K19/00 C07K17/02 C12Q1/533
C12N1/21 //C07K103:00,C07K101:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STOVER C K ET AL: "COMPLETE GENOME SEQUENCE OF PSEUDOMONAS AERUGINOSA PA01, AN OPPORTUNISTIC PATHOGEN" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 406, no. 6799, 31 August 2000 (2000-08-31), pages 959-964, XP000996980 ISSN: 0028-0836 The full genomic sequence was diclosed and could be retrieved at www.pseudomonas.com; the Swall entry ID TPIS_PSEAE shows 100% identity with SEQ ID N°2 and 99.2% identity with claimed SEQ ID N°4 ---	1-41, 56-69,71

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2003	21/08/2003

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WILLIAMS JOHN C ET AL: "Structural and mutagenesis studies of leishmania triosephosphate isomerase: A point mutation can convert a mesophilic enzyme into a superstable enzyme without losing catalytic power." PROTEIN ENGINEERING, vol. 12, no. 3, March 1999 (1999-03), pages 243-250, XP002250090 ISSN: 0269-2139 page 244-246	1-41, 56-69,71
Y	VELANKER SAMEER S ET AL: "Triosephosphate isomerase from Plasmodium falciparum: The crystal structure provides insights into antimalarial drug design." STRUCTURE (LONDON), vol. 5, no. 6, 1997, pages 751-761, XP009015082 ISSN: 0969-2126 see Material and methods and pages 751-752, 758	1-41, 56-69,71
Y	WIERENGA R K ET AL: "COMPARISON OF THE REFINED CRYSTAL STRUCTURES OF LIGANDED AND UNLIGANDED CHICKEN YEAST AND TRYPANOSOMAL TRIOSEPHOSPHATE ISOMERASE" JOURNAL OF MOLECULAR BIOLOGY, vol. 224, no. 4, 1992, pages 1115-1126, XP009015108 ISSN: 0022-2836 the whole document	1-41, 56-69,71
Y	NIENABER VICKI L ET AL: "Discovering novel ligands for macromolecules using X-ray crystallographic screening." NATURE BIOTECHNOLOGY, vol. 18, no. 10, October 2000 (2000-10), pages 1105-1108, XP002250092 ISSN: 1087-0156 the whole document	40,41, 56-69,71
Y	GSCHWEND D A ET AL: "MOLECULAR DOCKING TOWARDS DRUG DISCOVERY" JOURNAL OF MOLECULAR RECOGNITION, HEYDEN & SON LTD., LONDON, GB, vol. 9, 1996, pages 175-186, XP000882526 ISSN: 0952-3499 the whole document	19,25, 28-32, 36-41, 56-69,71

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 70955 A (YAMAMOTO ROBERT T ;OHLSEN KARI L (US); WALL DANIEL (US); XU H HOWA) 27 September 2001 (2001-09-27) Protein in exmaple 3, SEQ ID N°12053 shows 100% identity with SEQ ID N°2 in 251 aa overlap. ---	1-41, 56-69,71
P,Y	JOUBERT F ET AL: "Structure-based inhibitor screening: A family of sulfonated dye inhibitors for malaria parasite triosephosphate isomerase." PROTEINS, vol. 45, no. 2, 1 November 2001 (2001-11-01), pages 136-143, XP009015107 ISSN: 0887-3585 especially page 137-139 and Fig. 7 ---	1-41, 56-69,71
A	FLEISCHMANN WOLFGANG ET AL: "A novel method for automatic functional annotation of proteins." BIOINFORMATICS (OXFORD), vol. 15, no. 3, March 1999 (1999-03), pages 228-233, XP002250093 ISSN: 1367-4803 the whole document ---	1-12
P,A	BRENNER STEVEN E: "A tour of structural genomics." NATURE REVIEWS GENETICS, vol. 2, no. 10, October 2001 (2001-10), pages 801-809, XP002250126 ISSN: 1471-0056 the whole document -----	1-41, 56-69,71

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 02/01453

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 42-55, 70, 72-75
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(v) PCT - Presentation of information

2. [X] Claims Nos.: 42-55, 70, 72-75
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 42-55, 70, 72-75

Concerning claims 42-55, 70, 72-75 applicant's attention is drawn to Rule 67(v) PCT. The subject-matter of claims 42-55, 70, 72-75 refers to the presentation of structure data (a structure model of the P. aeruginosa triosephosphate isomerase), scalable three-dimensional configuration of points, and is not regarded as patentable invention within the meaning of Rule 67 (v) PCT since it relates to a presentation of information (protein model structure coordinates or configuration of points characterised by coordinates) as a coordinate listings, or information stored on a computer or computer readable media. Thus, the above mentioned claims will not be searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/01453

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0170955 A	27-09-2001	AU 4934501 A	03-10-2001
		CA 2404260 A1	27-09-2001
		EP 1268774 A2	02-01-2003
		WO 0170955 A2	27-09-2001
		US 2002061569 A1	23-05-2002

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